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

TELSAR AMH

1. Generic Name

Telmisartan, Amlodipine & Hydrochlorothiazide Tablets 40/5/12.5

Telmisartan, Amlodipine & Hydrochlorothiazide Tablets 80/5/12.5

2. Qualitative and quantitative Composition:

TELSAR AMH 40/5/12.5

Each Film Coated Tablet Contains:

Telmisartan I.P. ……..…40 mg

Amlodipine Besilate I.P.

Eq. to Amlodipine ……..5 mg

Hydrochlorothiazide I.P. ……...12.5 mg

Excipients……..…….q.s.

Colours: Titanium Dioxide I.P.

The Excipients used are Pregelatinized Starch I.P., Microcrystalline Cellulose I.P., Sodium Starch Glycolate I.P., Hydroxy Propyl Cellulose I.P., Dibasic Calcium Phosphate I.P., Polyvinyl Pyrrrolidone I.P., Isopropyl Alcohol I.P., Croscarmellose Sodium I.P., Talcum I.P., Colloidal Silicon Dioxide I.P., Sodium Lauryl Sulphate I.P., HPMC E15, Methylene Chloride I.P., PEG 6000 I.P.

TELSAR AMH 80/5/12.5

Each Film Coated Tablet Contains:

Telmisartan I.P. ……..…80 mg

Amlodipine Besilate I.P.

Eq. to Amlodipine ……..5 mg

Hydrochlorothiazide I.P. ……...12.5 mg

Excipients……..…….q.s.

Colours: Titanium Dioxide I.P.

The Excipients used are Pregelatinized Starch I.P., Microcrystalline Cellulose I.P., Sodium Starch Glycolate I.P., Hydroxy Propyl Cellulose I.P., Dibasic Calcium Phosphate I.P., Polyvinyl Pyrrrolidone I.P., Isopropyl Alcohol I.P., Croscarmellose Sodium I.P., Talcum I.P., Colloidal Silicon Dioxide I.P., Sodium Lauryl Sulphate I.P., HPMC, Methylene Chloride 85 I.P., PEG 6000 I.P.

3. Dosage form and strength

Dosage form: Film Coated Tablet

Strength: Telmisartan, Amlodipine & Hydrochlorothiazide Tablets 40 mg+5 mg+12.5 mg and 80 mg +5 mg+12.5 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the treatment of patients with Hypertension.

4.2 Posology and method of administration

Posology

Dose: As directed by the Physician.

Usual Dose: 1 tablet of TELSAR AMH to be administered once daily. Adjust dosage according to blood pressure goals. If adequate response is not achieved after 2 to 4 weeks of therapy, dose may be increased. The dosage, however, should be individualized.

Dosage of individual drugs should not exceed the recommended maximum daily doses.

- Telmisartan efficacy is dose-related over the range of 20 to 80 mg per day.
- Hydrochlorothiazide is effective in doses of 12.5 mg to 50 mg once daily.
- Amlodipine is effective over the range of 2.5 mg to 10 mg once daily.

If blood pressure remains uncontrolled, consider a change to more appropriate treatment.
TELSAR AMH Tablets may be administered with or without food. The tablet should be swallowed whole with water and not to be cut, crushed or chewed.

Method of administration

Tablet for oral administration.

4.3 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)

4.4 Special warnings and precautions for use

Telmisartan

Fetal Toxicity

When pregnancy is detected, Telmisartan should be discontinued as soon as possible, it can cause injury and even death to the developing fetus, when used during second and third trimesters of pregnancy.

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, Amlodipine & Hydrochlorothiazide Tablets should not 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. In addition, Telmisartan and Hydrochlorothiazide should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with Telmisartan and Hydrochlorothiazide in patients with hepatic impairment. Due to the half-life of amlodipine, slow dose titration and careful monitoring may be required in patients with severe 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.

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

Telmisartan and Hydrochlorothiazide must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min). There is no experience regarding the administration of Telmisartan and Hydrochlorothiazide in patients with recent kidney transplantation. Experience with Telmisartan and Hydrochlorothiazide is modest in the patients with mild to moderate renal impairment, therefore periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. Thiazide diuretic-associated azotaemia may occur in patients with impaired renal function. 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.

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, Amlodipine & Hydrochlorothiazide Tablets.

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, Amlodipine & Hydrochlorothiazide 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.

The safety and efficacy of amlodipine in hypertensive crisis has not been established. Patients with cardiac failure

Patients with heart failure

They 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.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance, whereas hypoglycaemia may occur in diabetic patients under insulin or antidiabetic therapy and telmisartan treatment. Therefore, in these patients blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated. Latent diabetes mellitus may become manifest during thiazide therapy.

An increase in cholesterol and triglyceride levels has been associated with thiazide diuretic therapy; however, at the dose 12.5 mg of Hydrochlorothiazide, minimal or no effects were reported.

Hyperuricemia may occur or frank gout may be precipitated in some patients receiving thiazide therapy.

Electrolyte imbalance

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (including hypokalaemia, hyponatraemia and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, asthenia, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.

- Hypokalaemia

Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with telmisartan may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greater in patients with cirrhosis of liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or Adrenocorticotropic hormone (ACTH).

- Hyperkalaemia

Conversely, due to the antagonism of the angiotensin II (AT_1) receptors by the telmisartan component of Telmisartan/Hydrochlorothiazide, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with Telmisartan and Hydrochlorothiazide, risk factors for the development of hyperkalaemia include renal insufficiency and/or heart failure, and diabetes mellitus. Potassium-sparing diuretics,

potassium supplements or potassium-containing salt substitutes should be co-administered cautiously with Telmisartan and Hydrochlorothiazide.

- Hyponatraemia and hypochloraemic alkalosis

There is no evidence that Telmisartan and Hydrochlorothiazide would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

- Hypercalcaemia

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

- Hypomagnesaemia

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Lactose Monohydrate

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of fructose intolerance and/or with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ethnic differences

As with all other angiotensin II receptor antagonists, telmisartan is apparently less effective in lowering blood pressure in black patients 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.

General

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics, including hydrochlorothiazide.

Cases of photosensitivity reactions have been reported with thiazide diuretics. If a photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Choroidal Effusion, Acute Myopia and Angle-Closure Glaucoma

Hydrochlorothiazide, a sulphonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC.

Elderly patients

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

4.5 Drugs interactions

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.

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.

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

Pregnancy

Telmisartan: Pregnancy Category D; Hydrochlorothiazide: Pregnancy Category B; Amlodipine: Pregnancy Category C.

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Thus, pregnant women with hypertension should be carefully monitored and managed accordingly.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics exposes mother and fetus to unnecessary hazards. There is limited experience with hydrochlorothiazide use during pregnancy, especially during the first trimester. The safety of

amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses of amlodipine. Telmisartan causes fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin aldosterone system (RAAS) during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Thus, TELSAR AMH Tablets are contraindicated during the second and third trimesters of pregnancy. When pregnancy is detected or planned, TELSAR AMH Tablets should be discontinued immediately and appropriate alternative therapy should be initiated.

Breast-feeding

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

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Telmisartan and Hydrochlorothiazide during breast-feeding is not recommended. If Telmisartan and Hydrochlorothiazide is used during breast-feeding, doses should be kept as low as possible.

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.

Paediatric Patients

The safety and efficacy of this combination therapy in children and adolescents below 18 years of age have not been established. Thus, TELSAR AMH Tablets are not recommended for use in paediatric population.

Fertility

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

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

Geriatric Patients

With telmisartan and hydrochlorothiazide, no overall differences in effectiveness and safety were observed in elderly patients compared to younger patients, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC; therefore, caution should be exercised. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant diseases and/or other drug therapy.

4.7 Effects on ability to drive and use machines

Telmisartan and Hydrochlorothiazide can have influence on the ability to drive and use machines. Dizziness or drowsiness may occasionally occur when taking Telmisartan and Hydrochlorothiazide.

4.8 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 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	Hypotension2, orthostatic hypotension
	Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Uncommon	Cough, rhinitis
	Very rare	Interstitial lung disease4
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 disorder3
	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 adverse reactions

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: https://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.

4.9 Overdose

Telmisartan and Hydrochlorthiazide

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. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

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.

The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

Symptoms

The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia, dizziness, vomiting, increase in serum creatinine, and acute renal failure have also been reported. Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemic) and hypovolaemia resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate arrhythmia associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

Treatment

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 overdose. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements 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 effective and specific angiotensin II receptor subtype 1 (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.

An 80 mg dose of telmisartan administered to healthy volunteers 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).

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides have an effect on the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Presumably, through blockade of the renin-angiotensin-aldosterone system, co-administration of telmisartan tends to reverse the potassium loss associated with these diuretics. With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6-12 hours.

5.2 Pharmacodynamic properties

Telmisartan

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 once daily dosing and includes the last 4 hours before the next dose.

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide class of diuretic agent. Hydrochlorothiazide is widely used to treat hypertension and edema. Acute antihypertensive effects of thiazides are thought to result from a reduction in blood volume and cardiac output, secondary to a natriuretic effect, although a direct vasodilatory mechanism has also been proposed. With chronic administration, plasma volume returns toward normal, but peripheral vascular resistance is decreased.

Thiazides do not affect normal blood pressure. Peak effect of hydrochlorothiazide is observed at about 4 hours of dosing and activity persists for up to 24 hours.

Amlodipine

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with intensity of elevated blood pressure at baseline (prior to treatment). Thus, individuals with moderate hypertension (diastolic pressure 105 to 114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90 to 104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg).

5.3 Pharmacokinetic properties

Telmisartan and Hydrochlorothiazide

Concomitant administration of telmisartan and hydrochlorothiazide does not appear to affect the pharmacokinetics of either substance in healthy subjects.

Absorption

Telmisartan: Following oral administration, peak concentrations of telmisartan are reached in 0.5 – 1.5 h after dosing. The absolute bioavailability of telmisartan at 40 mg and 160 mg was 42 % and 58 %, respectively. Food slightly reduces the bioavailability of telmisartan with a reduction in the area under the plasma concentration time curve (AUC) of about 6 % with the 40 mg tablet and about 19 % after a 160 mg dose. By 3 hours after administration plasma concentrations are similar whether telmisartan is taken fasting or with food. The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. Telmisartan does not accumulate significantly in plasma on repeated administration.

Hydrochlorothiazide: Following oral administration of Telmisartan and Hydrochlorothiazide peak concentrations of hydrochlorothiazide are reached in approximately 1.0 – 3.0 hours after dosing. Based on cumulative renal excretion of hydrochlorothiazide the absolute bioavailability was about 60 %.

Distribution

Telmisartan is highly bound to plasma proteins (>99.5 %) mainly albumin and alpha 1- acid glycoprotein. The apparent volume of distribution for telmisartan is approximately 500 litres indicating additional tissue binding.

Hydrochlorothiazide is 68 % protein bound in the plasma and its apparent volume of distribution is 0.83 – 1.14l/kg.

Biotransformation

Telmisartan is metabolised by conjugation to form a pharmacologically inactive acyl glucuronide. The glucuronide of the parent compound is the only metabolite that has been identified in humans. After a single dose of 14C-labelled telmisartan the glucuronide represents approximately 11 % of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Hydrochlorothiazide is not metabolised in man.

Elimination

Telmisartan: Following either intravenous or oral administration of 14C-labelled telmisartan most of the administered dose (>97 %) was eliminated in faeces via biliary excretion. Only minute amounts were found in urine. Total plasma clearance of telmisartan after oral administration is >1500 ml/min. Terminal elimination half-life was >20 hours.

Hydrochlorothiazide is excreted almost entirely as unchanged substance in urine. About 60 % of the oral dose is eliminated within 48 hours. Renal clearance is about 250 – 300 ml/min. The terminal elimination half-life of hydrochlorothiazide is 10 – 15 hours.

Linearity/non-linearity

Telmisartan: The pharmacokinetics of orally administered telmisartan are non-linear over doses from 20 – 160 mg with greater than proportional increases of plasma concentrations (Cmax and AUC) with increasing doses.

Hydrochlorothiazide exhibits linear pharmacokinetics.

Elderly

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

Gender

Plasma concentrations of telmisartan are generally 2 – 3 times higher in females than in males. In clinical trials however, no significant increases in blood pressure response or in the

incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary. There was a trend towards higher plasma concentrations of hydrochlorothiazide in female than in male subjects. This is not considered to be of clinical relevance.

Renal impairment

Renal excretion does not contribute to the clearance of telmisartan. Based on modest experience in patients with mild to moderate renal impairment (creatinine clearance of 30 – 60 ml/min, mean about 50 ml/min) no dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by haemodialysis. In patients with impaired renal function, the rate of hydrochlorothiazide elimination is reduced. In a typical study in patients with a mean creatinine, clearance of 90 ml/min the elimination half-life of hydrochlorothiazide was increased. In functionally nephric patients, the elimination half-life is about 34 hours.

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.

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

In preclinical safety studies performed with co-administration of telmisartan and hydrochlorothiazide in normotensive rats and dogs, doses producing exposure comparable to that in the clinical therapeutic range caused no additional findings not already observed with administration of either substance alone. The toxicological findings observed appear to have no relevance to human therapeutic use.

Toxicological findings also well-known from preclinical studies with angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists were: a reduction of red cell parameters (erythrocytes, haemoglobin, and haematocrit), changes of renal haemodynamic (increased blood urea nitrogen and creatinine), increased plasma renin activity, hypertrophy/hyperplasia of the juxtaglomerular cells and gastric mucosal injury. Gastric lesions could be prevented/ameliorated by oral saline supplementation and group housing of animals. In dog's renal tubular dilation and atrophy were observed. These findings are considered to be due to the pharmacological activity of telmisartan.

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.

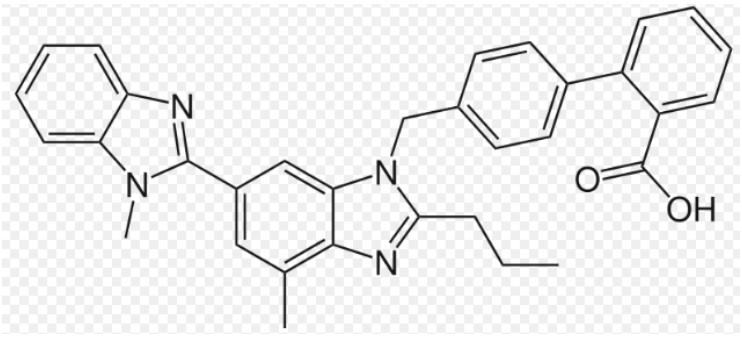
Telmisartan showed no evidence of mutagenicity and relevant clastogenic activity in in vitro studies and no evidence of carcinogenicity in rats and mice. Studies with hydrochlorothiazide have shown equivocal evidence for a genotoxic or carcinogenic effect in some experimental models. However, the extensive human experience with hydrochlorothiazide has failed to show an association between its use and an increase in neoplasms.

For the foetotoxic potential of the telmisartan/hydrochlorothiazide combination (see Fertility, pregnancy and lactation).

7. Description

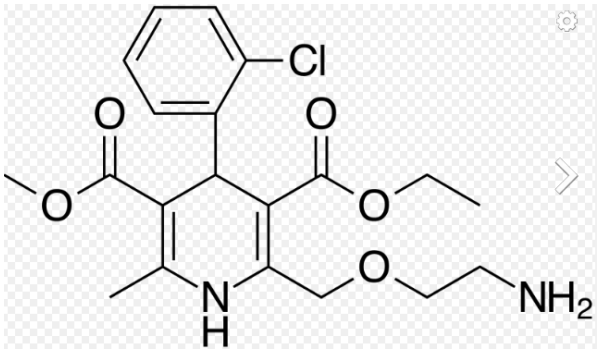
Telmisartan:

Telmisartan is 2-(4-{[4-Methyl-6-(1-methyl-1H-1,3-benzodiazol-2-yl)-2-propyl-1H-1,3-benzodiazol-1-yl]methyl}phenyl)benzoic acid. The Empirical formula is $C_{33}H_{30}N_4O_2$ and its molecular weight is 514.617 g/mol. The structural formula is:



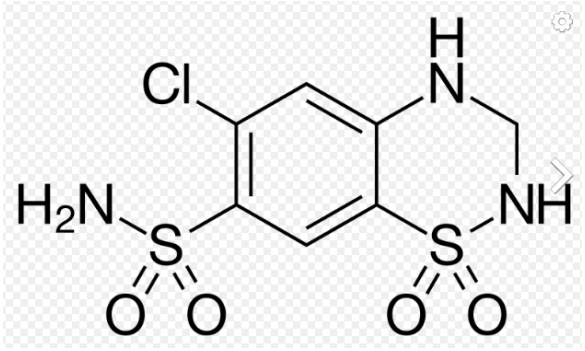
Amlodipine:

Amlodipine is (RS)-3-ethyl 5-methyl 2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate. The Empirical formula $C_{20}H_{25}ClN_2O_5$ and its molecular weight is 408.879 g/mol. The structural formula is:



Hydrochlorothiazide:

Hydrochlorothiazide is 6-chloro-1,1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide. The Empirical formula is $C_7H_8ClN_3O_4S_2$, and its molecular weight is 297.741 g/mol. The structural formula is:



8. Pharmaceutical particulars

8.1 Incompatibilities

Not Available

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

TELSAR AMH is available in pack of 10 Tablet.

8.4 Storage and handing instructions

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

Keep the medicine out of reach of children

Tablet should be swallowed whole & not to be chewed or crushed.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems

- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Pure & Cure Healthcare Pvt. Ltd.

Plot No. 26A, 27-30, Sector-8A, I.I.E.,

SIDCUL, Ranipur, Haridwar-249 403, Uttarakhand.

11. Details of permission or licence number with date

Mfg. Licence. No.: 31/UA/2013 Issued on: 31.05.2022

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

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Ahmedabad-380 009, INDIA

IN/TELSAR AMH 40 mg+5 mg+12.5 mg &80 mg +5 mg+12.5 mg/Apr-2024/01/PI