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

This package insert is continually updated: Please read carefully before using a new pack

TELSITE® am
Telmisartan & Amlodipine Tablets IP

COMPOSITION
Each uncoated tablet contains:
Telmisartan IP.....40 mg
Amlodipine Besilate I.P. equivalent to Amlodipine...5 mg
Excipients….q.s
Colour: Ferric oxide Red USP-NF

THERAPEUTIC INDICATIONS
For the treatment of essential hypertension.

DOSAGE & ADMINISTRATION
General

Posology
Patients receiving amlodipine and telmisartan from separate tablets can instead receive tablets of telmisartan/ amlodipine containing the same component doses. Patients should use the strength corresponding to their previous treatment.

The recommended dose is 1 tablet of telmisartan/ amlodipine daily.
The maximum daily dose of telmisartan is 80 mg and the maximum daily dose of amlodipine is 10 mg.

Special Populations

Pediatric patients

The safety and efficacy of telmisartan/ amlodipine in children aged below 18 years have not been established. No data are available.

Elderly patients

No dose adjustment is necessary for elderly patients. Caution is required when increasing the dosage. Little information is available in the very elderly patients.

Hepatic impairment

Dosage recommendations have not been established in patients with mild to moderate hepatic impairment. For telmisartan, the posology should not exceed 40 mg once daily. Telmisartan/ amlodipine is contraindicated in patients with severe hepatic impairment. In patients with mild to moderate hepatic impairment telmisartan/ amlodipine should be administered with caution.

Renal impairment

No posology adjustment is required for patients with mild to moderate renal impairment. Limited experience is available in patients with severe renal impairment or haemodialysis.

Caution is advised when using telmisartan/ amlodipine in such patients as amlodipine and telmisartan are not dialysable.

Administration

Telmisartan/ amlodipine can be taken with or without food. It is recommended to take telmisartan/amlodipine with some liquid.

CONTRAINDICATIONS

- Hypersensitivity to the active substances, to dihydropyridine derivatives, 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/ amlodipine with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).

WARNING AND PRECAUTIONS:

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 regarding the administration of telmisartan in patients with recent kidney transplantation. Telmisartan is not dialysable.

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.

As a consequence of inhibiting the renin-angiotensin-aldosterone system, hypotension, syncope, hyperkalaemia and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system by administering telmisartan with other blockers of the renin-angiotensin-aldosterone system) is therefore not recommended. Close monitoring of renal function is advisable if co-administration is considered necessary.

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 (cyclosporine or tacrolimus), and trimethoprim.
- Intercurrent events, in particular dehydration, 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.

Intestinal angioedema
Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists (see section ADVERSE REACTIONS). These patients presented with abdominal pain, nausea, vomiting and diarrhea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, **Telsite® am** should be discontinued, and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

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 ischemic cardiovascular disease could result in a myocardial infarction or stroke.

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

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

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

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

DRUG 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.

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

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

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

To be taken into account with concomitant use
Other antihypertensive agents
The blood pressure lowering effect of telmisartan can be increased by concomitant use of other antihypertensive medicinal products.

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.
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. Close clinical observation of patients is recommended 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).

Grapefruit and grapefruit juice
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. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

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

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

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

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

USE IN SPECIFIC POPULATIONS

PREGNANCY
Temisartan/amlodipine is not recommended during the first trimester of pregnancy as no data are available and safety profile has not been established for both amlodipine and telmisartan.
Temisartan/amlodipine is contraindicated during the second and third trimesters of pregnancy due to telmisartan content.

Telmisartan

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy.

There are no adequate data from the use of telmisartan in pregnant women. 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, 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, 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.

Amlodipine
The safety of amlodipine in human pregnancy has not been established.
In animal studies, reproductive toxicity was observed at high doses.
Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

LACTATION
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. No information is available regarding the use of telmisartan during breast-feeding. Therefore, temisartan/amlodipine is not recommended and alternative treatments with better established safety profiles during breast feeding are preferable, especially while breast-feeding a newborn or preterm infant.

FERTILITY

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

Amlodipine
Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS

Temisartan/amlodipine has moderate influence on the ability to drive and use machines. If patients taking temisartan/amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Therefore, caution should be recommended when driving a car or using machines. If patients experience these adverse reactions, they should avoid potentially hazardous tasks such as driving or using machines.

ADVERSE REACTIONS:
Adverse reactions previously reported with one of the individual components (amlodipine or telmisartan) may be potential undesirable effects with temisartan/amlodipine.

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

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

in patients treated for the reduction of cardiovascular morbidity was consistent with that obtained in hypertensive patients.

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

Tabulated summary 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), not known (cannot be estimated from the available data).

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

MedDRA system organ class	Frequency	Adverse reaction
Infections and infestations	Uncommon	Urinary tract infection including cystitis, upper respiratory tract infection including pharyngitis and sinusitis
	Rare	Sepsis including fatal outcome[1]
Blood and the lymphatic system disorders	Uncommon	Anaemia
	Rare	Eosinophilia, thrombocytopenia
Immune system disorders	Rare	Anaphylactic reaction, hypersensitivity
Metabolism and nutrition disorders	Uncommon	Hyperkalaemia
	Rare	Hypoglycaemia (in diabetic patients)
Psychiatric disorders	Uncommon	Insomnia, depression
	Rare	Anxiety
Nervous system disorders	Uncommon	Syncope
	Rare	Somnolence
Eye disorders	Rare	Visual disturbance
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Uncommon	Bradycardia
	Rare	Tachycardia
Vascular disorders	Uncommon	Hypotension[2], orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea, cough
	Very rare	Interstitial lung disease[4]
Gastrointestinal disorders	Uncommon	Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting
	Rare	Dry mouth, stomach discomfort, dysgeusia
	Not known	Intestinal angioedema
Hepatobiliary disorder	Rare	Hepatic function abnormal/liver disorder[3]
Skin and subcutaneous tissue disorders	Uncommon	Pruritus, hyperhidrosis, rash
	Rare	Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption
	Not Known	Cutaneous pseudolymphoma[i]ii, Lichenoid drug eruptioniii
Muscoloskeletal and connective tissue disorders	Uncommon	Back pain (e.g. sciatica), muscle spasms, myalgia
Renal and urinary disorders	Rare	Arthralgia, pain in extremity, tendon pain (tendinitis like symptoms)
	Uncommon	Renal impairment including acute renal failure
General disorders and administration site conditions	Uncommon	Chest pain, asthenia (weakness)
	Rare	Influenza-like illness
Investigations	Uncommon	Blood creatinine increased
	Rare	Haemoglobin decreased, blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased

1, 2, 3, 4 For further descriptions, please see sub-section “Description of selected adverse reactions”.

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

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

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

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

Intestinal angioedema
Cases of intestinal angioedema have been reported after the use of angiotensin II receptor antagonists (See section **WARNING AND PRECAUTIONS**).

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

Tabulated list of adverse reactions
The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥1/10,000 to <1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA System organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Very rare	Leukocytopaenia, thrombocytopaenia
Immune system disorders	Very rare	Allergic reactions
Metabolism and nutrition disorders	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Insomnia, mood changes (including anxiety), depression
	Rare	Confusion
Nervous system disorders	Common	Somnolence, dizziness, headache (especially at the beginning of the treatment)
	Uncommon	Tremor, dysgeusia, syncope, hypoesthesia, paraesthesia
	Very rare	Hypertonia, peripheral neuropathy
	Not known	Extrapyramidal disorder
Eye disorders	Common	Visual disturbance (including diplopia)
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Common	Palpitations

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

* Mostly consistent with cholestasis.

CLINICAL TRIALS

POSTMARKETING

Table 1. Adverse reactions with Telmisartan

Skin and subcutaneous tissue disorders	
Not known	Psoriasis and psoriasis exacerbationiv

OVERDOSE

Signs and symptoms

There is no experience of overdose with telmisartan/amlodipine. Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported. Non-cardiogenic pulmonary

oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors. 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

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 of both telmisartan and amlodipine.

Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position with elevation of extremities, with salt and volume replacement given quickly. 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.

PHARMACOLOGY

Mechanism Of Action

Telmisartan

Mechanism of action

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

Mechanism of action

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).

Pharmacodynamics

Telmisartan/amlodipine combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and telmisartan to the angiotensin II antagonist class of medicines. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

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.

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.

Pharmacokinetics

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.

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.

Metabolism

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.

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.

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).

Special populations

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.

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.

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.

Amlodipine

Absorption

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%.

Distribution

The volume of distribution is approximately 21 l/kg. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

The bioavailability of amlodipine is not affected by food intake.

Metabolism

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.

Elimination

Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.
Amlodipine is not dialysable.

Special populations

Elderly

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.

Hepatic Impairment

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40 – 60%.

Pharmacogenomics

CYP polymorphism

MANUFACTURED BY:
Windlas Biotech Private Limited (Plant-2), Khasra No.141 to 143 &145, Mohabewala Industrial Area, Dehradun-248110, Uttarakhand

MARKETED BY:
Sanofi India Limited, Sanofi House, C.T.S No-117-B, L& T Business Park, Saki Vihar Road, Powai, Mumbai 400 072- India

Updated: Feb 2025
Source: Amlodipine Besilate +Telmisartan Tablet CCDS Version 4 dated 12 Dec 2024