

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[®]

Telmisartan Tablets I.P.

COMPOSITION

Telsite[®] 20mg: Each uncoated tablet contains: Telmisartan IP.20 mg

Telsite[®] 40mg: Each uncoated tablet contains: Telmisartan IP.....40 mg

Telsite[®] 80mg: Each uncoated tablet contains: Telmisartan IP.....80 mg

THERAPEUTIC INDICATIONS

- Treatment of hypertension.
- For the prevention of cardiovascular morbidity and mortality in patient 55 years older at high risk of cardiovascular disease.

DOSAGE & ADMINISTRATION

Treatment of hypertension:

The usually effective dose is 40 mg once daily. Some patients may already benefit at a daily dose of 20 mg. In cases where the target blood pressure is not achieved, the dose of telmisartan can be increased to a maximum of 80 mg once daily. Alternatively, telmisartan may be used in combination with thiazide-type diuretics such as hydrochlorothiazide which has been shown to have an additive blood pressure lowering effect with telmisartan. When considering raising the dose, it must be borne in mind that the maximum antihypertensive effect is generally attained four to eight weeks after the start of treatment.

Cardiovascular prevention

The recommended dose is 80 mg once daily. It is not known whether doses lower than 80 mg of telmisartan are effective in reducing cardiovascular morbidity.

When initiating telmisartan therapy for the reduction of cardiovascular morbidity, close monitoring of blood pressure is recommended, and if appropriate adjustment of medications that lower blood pressure may be necessary.

Use in Specific Populations

Pediatric patients

The safety and efficacy of telmisartan in children and adolescents aged below 18 years have not been established. No recommendation on a posology can be made.

Elderly patients

No dose adjustment is necessary for elderly patients.

Hepatic impairment

Telmisartan is contraindicated in patients with severe hepatic impairment. In patients with mild to moderate hepatic impairment the posology should not exceed 40 mg once daily.

Renal impairment

Limited experience is available in patients with severe renal impairment or hemodialysis. A lower starting dose of 20 mg is recommended in these patients. No posology adjustment is required for patients with mild to moderate renal impairment.

Concomitant use of telmisartan with aliskiren is contraindicated in patients with renal impairment (GFR < 60 mL/min/1.73 m²).

Administration

Telmisartan tablets are for once-daily oral administration and should be taken with liquid, with or without food.

CONTRAINDICATIONS

1. Hypersensitivity to the active substance or to any of the excipients
2. Second and third trimesters of pregnancy
3. Biliary obstructive disorders
4. Severe hepatic impairment

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).

WARNINGS AND PRECAUTIONS

Pregnancy

Angiotensin II receptor antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA 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 AIIRAs 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.

Intravascular hypovolemia

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, diarrhea 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

The use of telmisartan in combination with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment ($\text{GFR} < 60 \text{ mL/min/1.73 m}^2$).

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalemia, and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system such as telmisartan has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

Primary aldosteronism

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

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Diabetic patients treated with insulin or antidiabetics

In these patients hypoglycemia 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.

Hyperkalemia

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

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, hyperkalemia 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 hyperkalemia 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 hyperkalemia are: salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non steroidal anti-inflammatory

medicinal products (NSAIDs including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus) and trimethoprim.

- Intercurrent events, in particular 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® 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 ischemic cardiopathy or ischemic cardiovascular disease could result in a myocardial infarction or stroke.

INTERACTIONS

Contraindicated

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

The combination of telmisartan with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment ($GFR < 60 \text{ mL/min/1.73 m}^2$) and is not recommended in other patients.

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

As with other medicinal products acting on the renin-angiotensin-aldosterone system, telmisartan may provoke hyperkalemia. The risk may increase in case of treatment combination with other medicinal products that may also provoke hyperkalemia: 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 hyperkalemia 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.

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.

Concomitant use not recommended

Potassium sparing diuretics or potassium supplements

AIIRAs such as telmisartan attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spironolactone, 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 hypokalemia 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 coadministration of angiotensin II receptor antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC₀₋₂₄ 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.

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.

REPRODUCTION

PREGNANCY

The use of AIIRAs is not recommended during the first trimester of pregnancy. The use of AIIRAs 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 AIIRAs, similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia). Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension.

LACTATION

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

FERTILITY

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

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS

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

ADVERSE REACTIONS

Summary of the safety profile

Serious adverse drug reactions include anaphylactic reaction and angioedema which may occur rarely ($\geq 1/10,000$ 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 ⁱ
Blood and the lymphatic system disorders	Uncommon	Anemia
	Rare	Eosinophilia, thrombocytopenia
Immune system disorders	Rare	Anaphylactic reaction, hypersensitivity
Metabolism and nutrition disorders	Uncommon	Hyperkalemia
	Rare	Hypoglycemia (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 ⁱⁱ , orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnea, cough
	Very rare	Interstitial lung disease ⁱⁱⁱ
Gastrointestinal disorders	Uncommon	Abdominal pain, diarrhea, dyspepsia, flatulence, vomiting
	Rare	Dry mouth, stomach discomfort, dysgeusia
	Not known	Intestinal angioedema
Hepato-biliary disorders	Rare	Hepatic function abnormal/liver disorder ^{iv}
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	Psoriasis and psoriasis exacerbation
Musculoskeletal and connective tissue disorders	Uncommon	Back pain (e.g. sciatica), muscle spasms, myalgia
	Rare	Arthralgia, pain in extremity, tendon pain (tendinitis like symptoms)
Renal and urinary disorders	Uncommon	Renal impairment including acute renal failure
General disorders and administration site conditions	Uncommon	Chest pain, asthenia (weakness)
	Rare	Influenza-like illness
Investigations	Uncommon	Blood creatinine increased
	Rare	Hemoglobin decreased, blood uric acid increased, hepatic enzyme increased, blood

		creatinine phosphokinase increased
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i,ii,iii,iv: for further descriptions, please see subsection “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.

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.

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.

Intestinal angioedema

Cases of intestinal angioedema have been reported after the use of angiotensin II receptor antagonists (see section WARNINGS AND PRECAUTIONS).

OVERDOSAGE

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

Signs and symptoms

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

Management

Telmisartan is not removed by hemodialysis. 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 replacement given quickly.

MECHANISM OF ACTION

Telmisartan is an orally active and specific angiotensin II receptor (type AT₁) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT₁ receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT₁ receptor. Telmisartan selectively binds the AT₁ receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT₂ and other less characterized 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.

MANUFACTURED BY

**Windlas Biotech Limited (Plant-IV),
Plot No. 183 & 192, 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**

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