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 Considerations
Telmisartan is an effective treatment of hypertension in once daily doses of 20-80 mg while amlodipine is effective in doses of 2.5-10 mg.

Dosage must be individualized and may be increased after at least 2 weeks. Most of the antihypertensive effect is apparent within 2 weeks and maximal reduction is generally attained after 4 weeks. The maximum recommended dose of telmisartan and amlodipine tablets is 80/10 mg once daily.

The adverse reactions of telmisartan are uncommon and independent of dose; those of amlodipine are a mixture of dose-dependent phenomena (primarily peripheral edema) and dose-independent phenomena, the former much more common than the latter.

Telmisartan and Amlodipine tablets may be taken with or without food.

Replacement Therapy
Patients receiving amlodipine and telmisartan from separate tablets may instead receive Telmisartan and Amlodipine tablets containing the same component doses once daily. When substituting for individual components, increase the dose of Telmisartan and Amlodipine tablets if blood pressure control has not been satisfactory.

Add-on Therapy for Patients with Hypertension Not Adequately Controlled on Antihypertensive Monotherapy
Telmisartan and amlodipine tablets may be used to provide additional blood pressure lowering for patients not adequately controlled with amlodipine (or another dihydropyridine calcium channel blocker) alone or with telmisartan (or another angiotensin receptor blocker) alone.

Patients treated with 10 mg amlodipine who experience any dose-limiting adverse reactions such as edema, may be switched to Telmisartan and Amlodipine tablets once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

Initial Therapy
A patient may be initiated on telmisartan and amlodipine tablets if it is unlikely that control of blood pressure would be achieved with a single agent. The usual starting dose of Telmisartan and Amlodipine tablets is 40/5 mg once daily.

Initial therapy with Telmisartan and Amlodipine tablets is not recommended in patients ≥75 years old or with hepatic impairment.

Correct imbalances of intravascular volume- or salt-depletion, before initiating therapy with Telmisartan and Amlodipine tablets.

Dosing in Specific Populations
Renal Impairment
No initial dosage adjustment is required for patients with mild or moderate renal impairment. Titrate slowly in patients with severe renal impairment.
Hepatic Impairment
In most patients, initiate amlodipine therapy at 2.5 mg. Titrate slowly in patients with hepatic impairment.
Patients 75 Years of Age and Older
In most patients, initiate amlodipine therapy at 2.5 mg. Titrate slowly in patients 75 years of age and older.

CONTRAINDICATIONS

- Known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan, amlodipine or any other component of this product.
- Do not co-administer aliskiren with Telsite am in patients with diabetes.

WARNING AND PRECAUTIONS:

Fetal Toxicity

WARNING: FETAL TOXICITY

- When pregnancy is detected, discontinue Telsite am as soon as possible
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Telsite am as soon as possible (*see Use in Specific Population).*

Hypotension
Telmisartan
In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with Telsite am tablets. Either correct this condition prior to administration of Telsite am tablets, or start treatment under close medical supervision with a reduced dose.

If hypotension does occur, place the patient in the supine position and, if necessary, give an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Amlodipine
Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

Hyperkalemia
Telmisartan
Hyperkalemia may occur in patients on ARBs (angiotensin renin blockers), particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk.

Patients with Impaired Hepatic Function

Telmisartan

As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Initiate telmisartan at low doses and titrate slowly in these patients [*see Dosage and Administration, Use in Specific Population]*

Amlodipine

Amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine at 2.5 mg in patients with hepatic impairment. The lowest dose of Telsite am tablet is 40/5 mg; therefore, initial therapy with Telsite am tablets is not recommended in hepatically impaired patients *(See Use in Specific Population).*

Renal Function Impairment

Telmisartan

As a consequence of inhibiting the renin-angiotensin-aldosterone system, anticipate changes in renal function in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with telmisartan.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of telmisartan in patients with unilateral or bilateral renal artery stenosis, but anticipate an effect similar to that seen with ACE inhibitors.

Dual Blockade of the Renin-Angiotensin-Aldosterone System

Telmisartan

Dual blockade of the renin angiotensin aldosterone system with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

In most patients no benefit has been associated with using two renin angiotensin aldosterone system inhibitors concomitantly. In general, avoid combined use of renin angiotensin aldosterone system inhibitors. Closely monitor blood pressure, renal function, and electrolytes in patients on Telsite am and other agents that affect the renin angiotensin aldosterone system.

Do not co-administer aliskiren with Telsite am in patients with diabetes. Avoid concomitant use of aliskiren with Telsite am in patients with renal impairment (GFR <60 mL/min/1.73 m^2).

Risk of Myocardial Infarction or Increased Angina

Amlodipine

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of Telsite am, particularly in patients with severe obstructive coronary artery disease.

Heart Failure

Amlodipine

Closely monitor patients with heart failure.

DRUG INTERACTIONS

Drug Interactions with Telsite am Tablets

The pharmacokinetics of amlodipine and telmisartan are not altered when the drugs are co-administered.

No drug interaction studies have been conducted with Telsite am tablets and other drugs, although studies have been conducted with the individual amlodipine and telmisartan components of Telsite am tablets.

Drug Interactions with Telmisartan
Aliskiren: Do not co-administer aliskiren with Telsite am in patients with diabetes. Avoid use of aliskiren with Telsite am in patients with renal impairment (GFR<60 mL/min).

Digoxin: When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan for the purpose of keeping the digoxin level within the therapeutic range.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including telmisartan. Therefore, monitor serum lithium levels during concomitant use.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving telmisartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

Drug Interactions with Amlodipine
In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

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.

Immunosuppressants: Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of trough blood levels of cyclosporin and tacrolimus and dose adjustment when appropriate is recommended.

The following have no clinically relevant effects on the pharmacokinetics of amlodipine: cimetidine, grapefruit juice, magnesium and aluminium hydroxide antacid, sildenafil.

Amlodipine has no clinically relevant effects on the pharmacokinetics or pharmacodynamics of the following: atorvastatin, digoxin, warfarin.

CYP3A4 Inhibitors
Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors.

CYP3A4 Inducers
No information is available on the quantitative effects of CYP3A4 inducers (*e.g., carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone, rifampicin, St. John's Wort)* on amlodipine. Patients should be monitored for adequate clinical effect when amlodipine is co-administered with CYP3A4 inducers.

USE IN SPECIFIC POPULATIONS

PREGNANCY

Telsite am can cause foetal harm when administered to pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death.

Disease-associated maternal and/or embryo/fetal risk

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. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal adverse reactions

Use of drugs that act on the RAS in the second and third trimesters of pregnancy can result in the following: oligohydramnios, reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death. In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus.

In patients taking Telsite am during pregnancy, perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. If oligohydramnios is observed, discontinue Telsite am, unless it is considered lifesaving for the mother. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Closely observe infants with histories of *in utero* exposure to Telsite am for hypotension, oliguria, and hyperkalemia. If oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function *[see Use in Specific Populations]*.

LACTATION

There is no information regarding the presence of Telsite am or telmisartan in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that amlodipine is present in human milk. However, there is insufficient information to determine the effects of amlodipine on the breastfed infant. There is no available information on the effects of amlodipine on milk production.

Because of the potential for serious adverse reactions in the breastfed infant including hypotension, hyperkalemia and renal impairment, advise a nursing woman not to breastfeed during treatment with Telsite am.

PEDIATRIC USE

Safety and effectiveness of Telsite am in pediatric patients have not been established.

Neonates with a history of in utero exposure to Telsite am:

If oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

GERIATRIC USE

Telmisartan

No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Amlodipine

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 disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40% to 60%, and a lower initial dose may be required. Since patients age 75 and older have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5 mg to telmisartan.

The dose of Telsite am is 40/5 mg; therefore, initial therapy with Telsite am is not recommended in patients 75 years of age and older.

HEPATIC INSUFFICIENCY
Monitor carefully and uptitrate slowly in patients with biliary obstructive disorders or hepatic insufficiency. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5 mg to telmisartan. The dose of Telsite am is 40/5 mg; therefore, initial therapy with Telsite am tablets is not recommended in hepatically impaired patients.

OVERDOSAGE
Telmisartan
Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage with telmisartan tablets would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

Amlodipine
Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited.

If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output.. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

ADVERSE REACTIONS:
Clinical Trials Experience
The adverse reactions that occurred in the placebo-controlled factorial design trial in ≥2% of patients treated with telmisartan and amlodipine tablets and at a higher incidence in telmisartan and amlodipine treated patients (n=789) than placebo-treated patients (n=46) were peripheral edema (4.8% vs 0%), dizziness (3.0% vs 2.2%), and back pain (2.2% vs 0%). Edema (other than peripheral edema), hypotension, and syncope were reported in <2% of patients treated with telmisartan and amlodipine tablets.

In the placebo-controlled factorial design trial, discontinuation due to adverse events occurred in 2.2% of all treatment cells of patients in the telmisartan/amlodipine-treated patients and in 4.3% in the placebo-treated group.

The most common reasons for discontinuation of therapy were peripheral edema, dizziness, and hypotension (each ≤0.5%).

Peripheral edema is a known, dose-dependent adverse reaction of amlodipine, but not of telmisartan. In the factorial design study, the incidence of peripheral edema during the 8 week, randomized, double-blind treatment period was highest with amlodipine 10 mg monotherapy. The incidence was notably lower when telmisartan was used in combination with amlodipine 10 mg.

Post marketing Experience
The following adverse reactions have been identified during post-approval use of telmisartan or amlodipine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to telmisartan or amlodipine.

Telmisartan

The most frequently spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, and increased CPK, anaphylactic reaction, tendon pain (including tendonitis, tenosynovitis), drug eruption (e.g., toxic skin eruption mostly reported as toxicoderma, rash, and urticaria), hypoglycemia (in diabetic patients), and angioedema (with fatal outcome). Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including telmisartan.

Amlodipine
Gynecomastia has been reported infrequently and a causal relationship is uncertain. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.

Postmarketing reporting has also revealed a possible association between extrapyramidal disorder and amlodipine.

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