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

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

Telmisartan, Amlodipine & Hydrochlorothiazide Tablets
Telsite® AMH

DESCRIPTION
Active Ingredients
Telmisartan, Amlodipine & Hydrochlorothiazide

Therapeutic or Pharmacological Class
Antihypertensive

Pharmaceutical Form(s)
Bilayered Tablet

COMPOSITION
Each uncoated bilayered tablet contains:

Telmisartan IP	40mg
Amlodipine besylate IP equivalent to Amlodipine	5mg
Hydrochlorothiazide IP	12.5mg

Excipients qs
Colour : Ferric Oxide Yellow USP-NF & Lake of Indigo Carmine (in Amlodipine & Hydrochlorothiazide Layer)

INDICATION
For the treatment of essential hypertension.

This fixed dose combination is not indicated for initial therapy (see Dosage and Administration).

DOSAGE AND ADMINISTRATION
Dose once daily.

Telsite AMH may be substituted for its individually titrated components for patients on telmisartan, amlodipine, and hydrochlorothiazide.

Telsite AMH may be used as add-on/switch therapy to provide additional blood pressure lowering for patients not adequately controlled on agents from two of the following antihypertensive classes: angiotensin receptor blockers, calcium channel blockers, and diuretics at their maximally tolerated, labeled, or usual dose.

Special Populations:

Pediatric Use
Safety and effectiveness in paediatric patients has not been established

Geriatric Use
Telmisartan and Hydrochlorothiazide
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 or other drug therapy
Amlodipine
Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40–60%, and a lower initial dose may be required.

Patients with Renal Impairment
Safety and effectiveness in patients with severe renal impairment (CrCl ≤30 mL/min) have not been established. Not recommended in patients with severe renal impairment. No dose adjustment is required in patients with mild (CrCl 60 to 90 mL/min) or moderate (CrCl 30 to 60 mL/min) renal impairment.

Patients with Hepatic Impairment
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 and higher blood levels.
Hydrochlorothiazide
Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.
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 2.5mg. Since the dose of Telsite AMH is 40/5/12.5mg, Telsite AMH is not recommended in hepatically impaired patients.

CONTRAINDICATIONS:
Telsite AMH is contraindicated in patients with known hypersensitivity to any component of this product (see Warnings and Precautions), in patients with anuria. Do not co-administer with aliskiren in patients with diabetes (see Drug Interactions).

WARNINGS AND PRECAUTIONS

Fetal Toxicity

WARNING : FETAL TOXICITY
When pregnancy is detected, discontinue Telsite AMH 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 AMH as soon as possible.

Thiazides cross the placental barrier and appear in cord blood. Adverse reactions include fetal or neonatal jaundice, thrombocytopenia.

Hypotension
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 initialization of treatment with Telsite AMH. Correct volume or salt depletion prior to administration of Telsite AMH.

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

Impaired Renal Function
Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing oliguria, progressive azotemia, or acute renal failure on Telsite AMH. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Telsite AMH.

Patients with Hepatic Failure
Telsite AMH is not recommended in hepatically impaired patients.

Dual Blockade of the Renin-Angiotensin-Aldosterone System and Changes in Renal Function
Dual blockade of the renin-angiotensin-aldosterone system (RAS) with angiotensin blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and renal impairment.

In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on Telsite AMH and other agents that affect the RAS.
Do not co-administer aliskiren with Telsite AMH in patients with diabetes. Avoid concomitant use of aliskiren with Telsite AMH in patients with renal impairment (GFR <60 mL/min/1.73 m_2).

Electrolytes and Metabolic Disorders

Drugs, including telmisartan, that inhibit the renin-angiotensin system can cause hyperkalemia, particularly in patients with renal insufficiency, diabetes, or combination use with other angiotensin receptor blockers or ACE inhibitors and the concomitant use of other drugs that raise serum potassium levels.

Hydrochlorothiazide can cause hypokalemia and hyponatremia. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Hypomagnesemia can result in hypokalemia which may be difficult to treat despite potassium repletion. Monitor serum electrolytes periodically.

Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium.

Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. Because telmisartan decreases uric acid, telmisartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia.

Hypersensitivity Reaction
Hydrochlorothiazide
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.

Acute Myopia and Secondary Angle-Closure Glaucoma
Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in 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 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 sulfonamide or penicillin allergy.

Systemic Lupus Erythematosus
Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Postsympathectomy Patients
The antihypertensive effects of hydrochlorothiazide may be enhanced in the postsympathectomy patient.

Increased Angina or Myocardial Infarction
Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

Heart Failure
Closely monitor patients with heart failure

DRUG INTERACTIONS

Telmisartan and Hydrochlorothiazide

Agents Increasing Serum Potassium
Co-administration of telmisartan with other drugs that raise serum potassium levels may result in hyperkalemia. Monitor serum potassium in such patients.

Lithium
Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of thiazide diuretics or angiotensin II receptor antagonists, including telmisartan. Monitor lithium levels in patients receiving Telsite AMH and lithium.

Digoxin
When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. Monitor digoxin levels in patients taking concomitant Telsite AMH and digoxin.

Aliskiren
Do not co-administer aliskiren with Telsite AMH in patients with diabetes. Avoid use of aliskiren with Telsite AMH in patients with renal impairment.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors):
Telmisartan
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 ARBs, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. The antihypertensive effect of ARBs may be attenuated by NSAIDs. Therefore, monitor renal function periodically in patients receiving Telsite AMH and NSAIDs.

Hydrochlorothiazide
Administration of a non-steroidal anti-inflammatory agent, including a selective COX-2 inhibitor, can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics. Therefore, when Telsite AMH and nonsteroidal anti-inflammatory agents including selective COX-2 inhibitors are used concomitantly, observe closely to determine if the desired effect of the diuretic is obtained.

Antidiabetic drugs (oral agents and insulin)
Dosage adjustment of the antidiabetic drug may be required when co-administered with hydrochlorothiazide.

Cholestyramine and Colestipol resins

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Stagger the dosage of hydrochlorothiazide and the resin such that hydrochlorothiazide is administered at least 4 hours before or 4 to 6 hours after the administration of the resin.

Amlodipine

CYP3A4 Inhibitors

Co-administration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors to determine the need for dose adjustment.

CYP3A4 Inducers

No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A4 inducers.

Sildenafil

Monitor for hypotension when sildenafil is co-administered with amlodipine.

Simvastatin

Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. 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 cyclosporine and tacrolimus is recommended and adjust the dose when appropriate.

PREGNANCY

Telsite AMH can cause fetal harm when administered to a 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.

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 patients taking Telsite AMH 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 AMH, 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 AMH for hypotension, oliguria, andhyperkalemia. 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 replacing renal function.

LACTATION

There is no information regarding the presence of Telsite AMH or telmisartan in human milk, the effects on the breastfed infant or the effects on milk production.

Telmisartan is present in the milk of lactating rats. 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 AMH.

ADVERSE REACTIONS

Telmisartan and hydrochlorothiazide

The following adverse reactions are discussed elsewhere in labeling:

- Hypotension
- Renal Impairment
- Electrolytes and Metabolic Disorders

Common adverse effects ≥2%: Fatigue, influenza like symptoms, dizziness, nausea, diarrhea, sinusitis and upper respiratory tract infection.

The most common adverse reaction to amlodipine is oedema which occurred in dose related manner. Other adverse experiences not dose related but reported with an incidence >1.0% are fatigue, nausea, abdominal pain and somnolence.

OVERDOSAGE:

Telmisartan

Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage with telmisartan 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.

Hydrochlorothiazide

The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD_{50} of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

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, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. 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.

STORAGE CONDITIONS
Store in a dry place at a temperature not exceeding 30ºC protected from light.

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 Bussiness Park, Saki Vihar Road,Powai, Mumbai 400 072- India

Created: June 2018

Reference:

- Micardis® HCT (Boehringer Ingelheim Pharmaceuticals) US PI dated February 2018 accessed in June 2018
- Twynsta Leaflet (Boehringer Ingelheim Pharmaceuticals) dated February 2018 accessed on 6th June 2018
- Norvasc® (Pfizer) US PI dated October 2017 accessed in June 2018