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

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Telmisartan, Hydrochlorothiazide and Amlodipine Besylate Tablets
(Brand Name: XSTAN®-AMH Tablets)

2. Qualitative and Quantitative Composition

Each Uncoated Bilayered Tablet Contains:
Telmisartan IP ……..… 40 mg
Hydrochlorothiazide IP …….. 12.5 mg
Amlodipine Besylate IP equivalent to Amlodipine ……. 5 mg
Excipients …… q.s.
Colours: Sunset Yellow FCF

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Telmisartan 40 mg, Hydrochlorothiazide 12.5 mg, and Amlodipine 5 mg per tablets.

4. Clinical Particulars

4.1 Therapeutic Indication

XSTAN-AMH Tablets are indicated for the treatment of essential hypertension in adults, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
XSTAN-AMH Tablets are usually administered in patients whose blood pressure is not adequately controlled on dual drug combination therapy.

4.2Posology and Method of Administration

For oral administration in adults.
Usual Dose: 1 tablet of XSTAN-AMH to be administered once daily. Adjust dosage according to blood pressure goals. If adequate response is not achieved after 2 to 4 weeks of therapy, dose may be increased. The dosage, however, should be individualized.
Dosage of individual drugs should not exceed the recommended maximum daily doses.

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

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

Or, as prescribed by the physician.

4.3Contraindications

XSTAN-AMH Tablets are contraindicated in the following:

- Hypersensitivity to telmisartan or to hydrochlorothiazide or to amlodipine or to any component of the product.
- Severe hepatic impairment, cholestasis, and biliary obstructive disorders.
- Severe renal impairment (creatinine clearance <30 ml/min).
- Refractory hypokalaemia, hypercalcaemia, and hyponatraemia.
- In patients with anuria.
- Second and third trimesters of pregnancy.
- Severe hypotension.
- Cardiogenic shock.
- Significant aortic stenosis.
- Hemodynamically unstable heart failure after acute myocardial infarction.
- The concomitant use of telmisartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).

4.4Special Warnings and Precautions for Use

Telmisartan

Fetal Toxicity: Use of drugs that act on the renin angiotensin aldosterone system (RAAS) during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. 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. Thus, when pregnancy is detected, discontinue telmisartan as soon as possible.

Hypotension: In patients with an activated RAAS, 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 telmisartan. Either correct this condition prior to administration of telmisartan, or start treatment under close medical supervision with a reduced dose.

Hyperkalemia: Hyperkalemia may occur in patients on angiotensin receptor blockers/antagonists (ARBs), 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.

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 drugs that affect the RAAS.

Dual Blockade of the RAAS: There is evidence that the concomitant use of angiotensin-converting enzyme (ACE) inhibitors, ARBs or aliskiren increases the risk of hypotension, hyperkalemia, and decreased renal function (including acute renal failure). Dual blockade of

RAAS through combined use of ACE-inhibitors, ARBs or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and be subject to close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy. Do not co-administer aliskiren with telmisartan in patients with diabetes or renal impairment.

Other Body Functions Depends on the Activation of RAAS: As a consequence of inhibiting the RAAS, changes in renal function in susceptible individuals may be anticipated. In patients whose vascular tone and renal function depend predominantly on the activity of the RAAS (e.g., patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with drugs which affect this system such as telmisartan has been associated with acute hypotension, azotemia, oliguria, or rarely acute renal failure.

Primary Aldosteronism: Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the RAAS. Therefore, 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 Antidiabetic Drugs: Hypoglycaemia may occur when telmisartan is co-administered with these drugs. Therefore, in these patients appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated.

Other Precautions: As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischemic cardiovascular disease could result in a myocardial infarction or stroke.

<u>Hydrochlorothiazide</u>

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 acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Seek immediate medical attention if patients experience any symptoms. 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.

Diabetes and Hypoglycemia: Latent diabetes mellitus may become manifest and diabetic patients given thiazides may require adjustment of their insulin dose.

Renal Disease: Cumulative effects of the thiazides may develop in patients with impaired renal function. In such patients, thiazides may precipitate azotemia.

Fluid and Electrolyte Imbalance: In published studies, clinically significant hypokalemia has been consistently less common in patients who received 12.5 mg of hydrochlorothiazide than in patients who received higher doses. Nevertheless, periodic determination of serum electrolytes should be performed in patients who may be at risk for the development of

hypokalemia. Patients should be observed for signs of fluid or electrolyte disturbances, i.e., hyponatremia, hypochloremic alkalosis, and hypokalemia and hypomagnesemia.

1) **Hypokalemia:** Hypokalemia may develop, especially with brisk diuresis when severe cirrhosis is present, during concomitant use of corticosteroid or adrenocorticotropic hormone (ACTH) or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia and hypomagnesemia can provoke ventricular arrhythmias or sensitize or exaggerate the response of the heart to the toxic effects of digitalis. Hypokalemia may be avoided or treated by potassium supplementation or increased intake of potassium rich foods.
2) **Hyponatremia:** Dilutional hyponatremia is life-threatening and may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.
3) **Hyperuricemia:** Hyperuricemia or acute gout may be precipitated in certain patients receiving thiazide diuretics.

Warning signs or symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Impaired Hepatic Function: Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate hepatic coma in patients with severe liver disease.

Parathyroid Disease: Calcium excretion is decreased by thiazides. Also, pathologic changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy.

Amlodipine

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

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.

Patients with Hepatic Failure: Amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t½) is 56 hours in patients with impaired hepatic function. Thus, caution should be exercised and dose should be titrated slowly in patients with severe hepatic impairment.

4.5Drug Interactions

Telmisartan

Telmisartan is not metabolized by the cytochrome P450 enzymes and had no effects *in vitro* on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Thus, telmisartan is not expected to interact with drugs that inhibit or are metabolised by cytochrome P450 enzymes.

Aliskiren: Do not co-administer aliskiren with telmisartan in patients with diabetes. Avoid use of aliskiren with telmisartan in patients with renal impairment (GFR < 60 ml/min/1.73 m^2).

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

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

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 (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. Monitor renal function periodically in patients receiving telmisartan and NSAID therapy. The antihypertensive effect of ARBs (including telmisartan) may be attenuated by NSAIDs, including selective COX-2 inhibitors.

Potassium Sparing Diuretics or Potassium Supplements: Telmisartan attenuates 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 hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

Other Drugs: Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin, or ibuprofen.

<u>Hydrochlorothiazide</u>

When administered concurrently, the following drugs may interact with thiazide diuretics:

Alcohol, Barbiturates, or Narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic Drugs (Oral Agents and Insulin): Dosage adjustment of the antidiabetic drug may be required.

Other Antihypertensive Drugs: Additive antihypertensive effect may occur, thus, reduction in dosage is required.

Cholestyramine and Colestipol Resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 %, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor Amines (e.g., Norepinephrine): Possible decreased response to pressor amines, but not sufficient to preclude their use.

Skeletal Muscle Relaxants (e.g., Tubocurarine): Possible increased responsiveness to the muscle relaxants such as curare derivatives.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): In some patients, administration of NSAID can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.

Digoxin: Thiazide-induced hypokalemia or hypomagnesemia may predispose the patient to digoxin toxicity.

Lithium: Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and greatly increase the risk of lithium toxicity.

Laboratory Test Interactions: Thiazides should be discontinued before carrying out tests for parathyroid function.

Amlodipine

1) Impact of Other Drugs on Amlodipine

Sildenafil: Hypotensive effect is enhanced when amlodipine is given with sildenafil. Monitor for hypotension when these drugs are given together.

CYP3A Inhibitors (e.g., Ketoconazole, Itraconazole, Diltiazem, Erythromycin, Fluconazole, etc.): Co-administration with CYP3A inhibitors 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 CYP3A inhibitors to determine the need for dose adjustment.

CYP3A Inducers (e.g., Carbamazepine, Phenytoin, Rifampin, etc.): No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure and edema should be closely monitored when amlodipine is co-administered with CYP3A inducers.

2) Impact of Amlodipine on Other Drugs

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 blood levels of cyclosporine and tacrolimus and dosage adjustment (whenever appropriate) is recommended.

4.6Use in Special Populations

Pregnant Women

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

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

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics exposes mother and fetus to unnecessary hazards. There is limited experience with hydrochlorothiazide use during pregnancy, especially during the first trimester. The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive

toxicity was observed at high doses of amlodipine. Telmisartan causes fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin aldosterone system (RAAS) during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Thus, XSTAN-AMH Tablets are contraindicated during the second and third trimesters of pregnancy. When pregnancy is detected or planned, XSTAN-AMH Tablets should be discontinued immediately and appropriate alternative therapy should be initiated.

Lactating Women

Thiazides appear in human milk. Limited available data from a published clinical study reports that amlodipine is present in human milk. However, no adverse effects of amlodipine on the breastfed infant have been observed. There is no information regarding the presence of 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 including hypotension, hyperkalemia, and renal impairment in the breastfed infant, it is advised that a nursing mother should not breastfeed her child while on XSTAN-AMH therapy. Accordingly, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric Patients

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

Geriatric Patients

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

Renal Impairment Patients

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the hydrochlorothiazide may develop in patients with impaired renal function. With telmisartan, dosage adjustment is not required for patients with mild to moderate renal impairment. Limited experience is available in patients with severe renal impairment or hemodialysis. Patients on dialysis may develop orthostatic hypotension and thus, blood pressure should be closely monitored. XSTAN-AMH Tablets to be used with caution in patients with impaired renal function. Due to lack of safety data, XSTAN-AMH Tablets are not recommended in patients with severe renal impairment.

Hepatic Impairment Patients

With hydrochlorothiazide therapy, minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease. Amlodipine is extensively metabolized by the liver and the plasma elimination half-life increases in patients with impaired hepatic function. As the majority of telmisartan is eliminated by biliary excretion, telmisartan-containing preparations are not to be given to patients with cholestasis or biliary obstructive disorders or severe hepatic insufficiency. These patients can be expected to have reduced hepatic clearance for telmisartan. XSTAN-AMH Tablets should be used with caution in patients with impaired hepatic function. In these patients, lower initial dose is to be used and telmisartan dose should not exceed 40 mg once daily. XSTAN-AMH Tablets are contraindicated in patients with severe hepatic impairment.

4.7Effect on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed with this combination therapy. Dizziness, drowsiness headache, fatigue, or nausea may occasionally occur in patients taking antihypertensive therapy (such as amlodipine or telmisartan) which may impair patient's ability to react.

Amlodipine and hydrochlorothiazide can have minor or moderate influence on the ability to drive and use machines, particularly at the initiation of the therapy. Thus, caution is recommended while driving a vehicle or operating machinery.

4.8Undesirable Effects

Telmisartan

Clinical Trials Experience

Adverse events occurred at an incidence of ≥ 1% in patients treated with telmisartan and at a greater rate than in patients treated with placebo were upper respiratory tract infections (URTIs), sinusitis, pharyngitis, back pain, and diarrhea.

In addition, the adverse events occurred at a rate of ≥ 1%, but at least as frequent in the placebo group were influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea, and peripheral edema. The incidence of adverse reactions was not dose-related and showed no correlation with gender, age or race of the patients.

Adverse events that occurred in more than 0.3% patients treated with telmisartan monotherapy in controlled or open trials are as follows. It cannot be determined whether these events were causally related to telmisartan therapy.

Autonomic Nervous System: Impotence, increased sweating, flushing.

Body as a Whole: Allergy, fever, leg pain, malaise.

Cardiovascular: Palpitation, edema, angina pectoris, tachycardia, abnormal ECG.

Central Nervous System: Insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia.

Gastrointestinal: Flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, gastroesophageal reflux, nonspecific gastrointestinal disorders, toothache.

Metabolic: Gout, hypercholesterolemia, diabetes mellitus.

Musculoskeletal: Arthritis, arthralgia, leg cramps.

Psychiatric: Anxiety, depression, nervousness.

Infections: Fungal infection, abscess, otitis media.
Respiratory: Asthma, bronchitis, rhinitis, dyspnea, epistaxis.
Skin: Dermatitis, rash, eczema, pruritus.
Urinary: Increased micturition frequency, cystitis.
Vascular: Cerebrovascular disorder.
Special Senses: Abnormal vision, conjunctivitis, tinnitus, earache.
Laboratory Tests: Decrease in hemoglobin, increase in creatinine, elevations of liver enzymes may occur in patients treated with telmisartan.

Post-Marketing Experience
The most frequent spontaneously reported events included headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, angioneurotic edema, urticaria, hypersensitivity, increased sweating, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, increased blood pressure, aggravated hypertension, 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, increased uric acid, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, increased creatine phosphokinase (CPK), anaphylactic reaction, tendon pain (including tendonitis, tenosynovitis), drug 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 ARBs, including telmisartan.

Hydrochlorothiazide
Adverse events that have been reported with hydrochlorothiazide, without regard to causality, are listed below:
Body as a Whole: Weakness.
Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation.
Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.
Hypersensitivity: Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions.
Metabolic: Electrolyte imbalance, hyperglycemia, glycosuria, hyperuricemia.
Musculoskeletal: Muscle spasm.
Nervous System/Psychiatric: Restlessness.
Renal: Renal dysfunction, interstitial nephritis, renal failure.
Skin: Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis.
Special Senses: Transient blurred vision, xanthopsia.
Urogenital: Impotence.

Amlodipine

Most common adverse reactions reported with amlodipine are headache and pedal edema. Adverse effects with an incidence >1% in clinical studies included abdominal pain, nausea, dizziness, somnolence, flushing, palpitations, and fatigue.

Rare adverse events observed in controlled clinical trials or open trials or post-marketing surveillance studies (causal relationship is uncertain) included:

Autonomic Nervous System: Dry mouth, increased sweating, cold and clammy skin.

Cardiovascular: Arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural hypotension, vasculitis, cardiac failure, pulse irregularity, extrasystoles.

Central and Peripheral Nervous System: Hypoesthesia, peripheral neuropathy, paresthesia, tremor, vertigo, ataxia, hypertonia, migraine, apathy, agitation, amnesia.

Gastrointestinal: Anorexia, constipation, dysphagia, diarrhea, flatulence, gastritis, increased appetite, loose stools, pancreatitis, vomiting, gingival hyperplasia/hypertrophy.

General: Allergic reaction, back pain, hot flushes, malaise, pain, rigors, weight gain, weight loss.

Hemopoietic: Leukopenia, purpura, thrombocytopenia.

Metabolic and Nutritional: Hyperglycemia, thirst.

Musculoskeletal System: Arthralgia, arthrosis, muscle cramps, myalgia, muscle weakness, twitching.

Psychiatric: Sexual dysfunction, insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory System: Dyspnea, epistaxis, cough, rhinitis.

Skin and Appendages: Rash, pruritus, urticaria, angioedema, skin dryness, alopecia, skin discoloration.

Special Senses: Abnormal vision, conjunctivitis, diplopia, eye pain, abnormal visual accommodation, xerophthalmia, tinnitus, parosmia, taste perversion.

Urinary System: Increased micturition frequency, nocturia, dysuria, polyuria.

4.9Overdose

Telmisartan

Limited data are available with regard to overdose in humans. The most likely manifestation of overdose with telmisartan would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation.

If symptomatic hypotension occurs, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis. Management of overdose depends on the time since ingestion and the severity of 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.

Hydrochlorothiazide

The most common signs and symptoms observed 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.
In the event of overdose, symptomatic and supportive measures should be employed. Emesis should be induced or gastric lavage performed. Correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures. If required, give oxygen or artificial respiration for respiratory impairment. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

Amlodipine

Overdose might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdose 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.

5. Pharmacological Properties

5.1 Mechanism of Action

Telmisartan

Telmisartan is a selective AT_1 subtype angiotensin II receptor antagonist. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin aldosterone system (RAAS), with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.
There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT_1 receptor than for the AT_2 receptor.

Hydrochlorothiazide

Hydrochlorothiazide (HCTZ) is a thiazide class of diuretic drugs which blocks the reabsorption of sodium (Na^+) and chloride (Cl^-) ions, and it thereby increases the quantity of sodium traversing the distal tubule of nephron. By this mechanism, hydrochlorothiazide increases excretion of water (diuretic effect), reduces blood volume, and thereby decreases cardiac output. These effects help to reduce increased blood pressure. As hydrochlorothiazide has weak antihypertensive effect, it is usually combined with other antihypertensive drugs.
A portion of the additional sodium presented to the distal tubule of nephron is exchanged there for potassium (K^+) and hydrogen (H^+) ions. With continued use of hydrochlorothiazide and depletion of sodium, compensatory mechanisms tend to increase this exchange and may

produce excessive loss of potassium, hydrogen, and chloride ions (electrolyte imbalance). Hydrochlorothiazide also decreases the excretion of calcium (Ca^{++}) and uric acid, may increase the excretion of iodide and may reduce glomerular filtration rate.

Amlodipine

Amlodipine is a dihydropyridine class of long-acting calcium channel blocker – CCB (calcium antagonist). Amlodipine inhibits the transmembrane influx of calcium ions (Ca^{++}) into vascular smooth muscle and cardiac muscle.

Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Serum calcium concentration is not affected by amlodipine.

5.2Pharmacodynamic Properties

Telmisartan

After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4 to 8 weeks after the start of treatment and is sustained during long-term therapy.

The antihypertensive effect persists constantly over 24 hours after once daily dosing and includes the last 4 hours before the next dose.

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

Hydrochlorothiazide

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

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

Amlodipine

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

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly

patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with intensity of elevated blood pressure at baseline (prior to treatment).
Thus, individuals with moderate hypertension (diastolic pressure 105 to 114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90 to 104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg).

5.3Pharmacokinetic Properties

Telmisartan

The pharmacokinetics of orally administered telmisartan is nonlinear over the dose range 20 to 160 mg, with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses.

Absorption: Following oral administration, peak plasma concentration (C_{max}) of telmisartan is reached in 0.5 to 1 hour after dosing. Food slightly reduces the bioavailability of telmisartan. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg, the bioavailability was 42% and 58%, respectively.

Distribution: Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and α_1-acid glycoprotein. The volume of distribution for telmisartan is approximately 500 liters indicating additional tissue binding.

Metabolism: Telmisartan is metabolized by conjugation to form a pharmacologically inactive acyl glucuronide. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Excretion: Most of the orally administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amount (0.49%) was found in the urine. Total plasma clearance of telmisartan is >800 ml/min. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half-life of approximately 24 hours.

Hydrochlorothiazide

Absorption: Hydrochlorothiazide is well absorbed (65% to 75%) following oral administration. Absorption of hydrochlorothiazide is reduced in patients with congestive heart failure. Peak plasma concentrations are observed within 1 to 5 hours of dosing, and range from 70 to 490 ng/ml following oral doses of 12.5 to 100 mg.

Distribution: Plasma concentrations are linearly related to the administered dose. Concentrations of hydrochlorothiazide are 1.6 to 1.8 times higher in whole blood than in plasma. Plasma protein binding is approximately 40% to 68%.

Metabolism and Excretion: The plasma elimination half-life is 6 to 15 hours. Hydrochlorothiazide is eliminated primarily by renal pathways. Following oral doses of 12.5 to 100 mg, 55% to 77% of the administered dose appears in urine and greater than 95% of the absorbed dose is excreted in urine as unchanged drug. In patients with renal disease, plasma concentration of hydrochlorothiazide is increased and the elimination half-life is prolonged.

Amlodipine

Absorption: After oral administration of therapeutic doses, amlodipine produces peak plasma concentrations between 6 to 12 hours. Absolute bioavailability has been estimated to be between 64 to 90%. The bioavailability is not altered by the presence of food.

Distribution: The volume of distribution is approximately 21 l/kg. *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.
Metabolism: Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.
Excretion: Excretion from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

6. Nonclinical Properties

6.1 Animal Toxicology

Telmisartan

Carcinogenicity: There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m^2 basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of telmisartan. These same doses have been shown to provide average systemic exposures to telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD of telmisartan (80 mg/day).
Mutagenesis: Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella and E. coli (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test.
Impairment of Fertility: No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m^2 basis, the MRHD of telmisartan. This dose in the rat resulted in an average systemic exposure (telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day).
Teratogenicity: No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses of up to 45 mg/kg/day. In rabbits, embryo lethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day (approximately 12 times the maximum recommended human dose [MRHD] of 80 mg on a mg/m^2 basis). In rats, maternally toxic (reduced body weight gain and food consumption) telmisartan doses of 15 mg/kg/day (approximately 1.9 times the MRHD on a mg/m^2 basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. The no-observed effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are approximately 0.64 and 3.7 times, respectively, on a mg/m^2 basis, the MRHD of telmisartan (80 mg/day).

Hydrochlorothiazide

Carcinogenesis: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential

of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.
Mutagenesis: Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mcg/mL, and in the Aspergillus nidulans non-disjunction assay at an unspecified concentration.
Impairment of Fertility: Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.
Teratogenicity: Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg hydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus.

Amlodipine

Carcinogenesis: Rats and mice treated with amlodipine in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 amlodipine mg/kg/day, showed no evidence of a carcinogenic effect of the drug.
Mutagenesis: Mutagenicity studies conducted with amlodipine revealed no drug related effects at either the gene or chromosome level.
Impairment of Fertility: There was no effect on the fertility of rats treated orally with amlodipine (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times [based on body weight of 50 kg] the maximum recommended human dose of 10 mg/day on a mg/m^2 basis).
Teratogenicity: No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine at doses up to 10 mg amlodipine/kg/day (approximately 10 and 20 times the maximum recommended human dose based on body surface area, respectively) during their respective periods of major organogenesis. However for rats, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

7. Description

XSTAN-AMH Tablets are Orange / White coloured, oblong shaped, slightly biconvex uncoated bilayered tablet.

XSTAN-AMH Tablets contains 40 mg of telmisartan, 12.5 mg of hydrochlorothiazide, and 5 mg of amlodipine for oral administration in adults.

Telmisartan

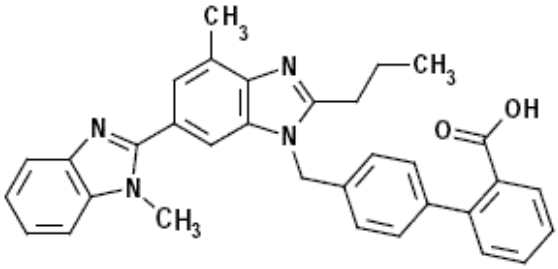
Telmisartan is an angiotensin II receptor (AT_1) antagonist class of antihypertensive agent. Telmisartan is a white to slightly yellowish solid. It is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid, and soluble in strong base.

Molecular Weight: 514.63 g/mol.

Molecular Formula: C33H30N4O2.

Chemical Name: 4'-[(1,4'-dimethyl-2'-propyl [2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid.

Structural Formula:



Hydrochlorothiazide

Hydrochlorothiazide is short acting thiazide class of diuretic used for the treatment of hypertension and congestive heart failure.

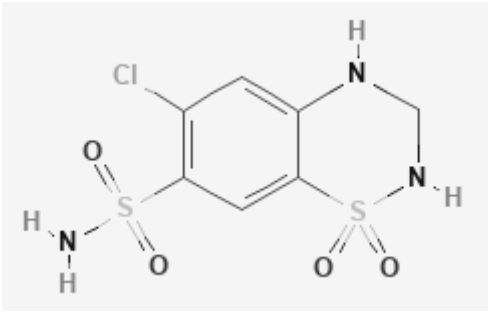
Hydrochlorothiazide is a white or practically white crystalline powder.

Molecular Weight: 297.7 g/mol.

Molecular Formula: C7H8ClN3O4S2.

Chemical Name: 6-chloro-1,1-dioxo-3,4-dihydro-2H-1λ6,2,4-benzothiadiazine-7-sulfonamide.

Structural Formula:



Amlodipine Besylate

Amlodipine Besylate is the besylate salt of amlodipine. Amlodipine is a long-acting calcium channel blocker (CCB) of a synthetic dihydropyridine class with antihypertensive and antianginal effects.

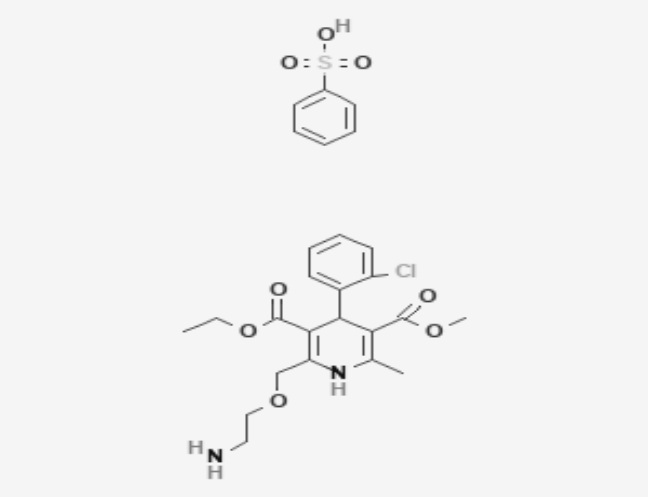
Amlodipine besylate is a white crystalline powder.

Molecular Weight: 567.1 g/mol.

Molecular Formula: C20H25ClN2O5•C6H6O3S.

Chemical Name: 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(2- chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate.

Structural Formula:



Inactive ingredients (excipients) of XSTAN-AMH Tablets contain Mannitol, Microcrystalline Cellulose, Crosscarmellose Sodium, Sodium Hydroxide (Pellets), Povidone K-30, Propanol M, Magnesium Stearate, Sodium Starch Glycolate, Colour Lake Sunset Yellow, Dicalcium Phosphate, Colloidal Silicon Dioxide & Talc.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 Months

8.3Packaging Information

15 tablets per strip.

8.4Storage and Handling Instructions

Store protected from light and moisture at a temperature not exceeding 25°C.
Keep out of reach of children.

9. Patient Counseling Information

Instructions to Patients

- Instruct patients to take this medicine exactly as prescribed by your doctor. Do not change the dose or stop therapy without consulting doctor.
- Patients are advised to take XSTAN-AMH Tablets once a day at any time of day at about the same time each day with or without food. Swallow tablets whole with water and strictly no to cut, crush or chew.
- If patients miss a dose, they can take it as soon as they remember. Do not take XSTAN-AMH Tablets if it has been more than 12 hours since the last missed dose. Wait and take the next dose at regular time; do not take 2 doses to make up for the missed doses.

- Pregnant women should strictly avoid use of this medicine. When pregnancy is detected or planned, discontinue XSTAN-AMH Tablets as soon as possible.
- Advise nursing mothers to avoid use of this medicine during lactation or not to breastfeed their infants during treatment.
- Use of this medicine is not recommended in children.
- Patients are advised not to take XSTAN-AMH Tablets if they have severe liver dysfunction or cholestasis or biliary obstructive disorders.
- Patients should be informed that while taking XSTAN-AMH Tablets do not stop taking other prescription medicines, including any other blood pressure medicines, without consulting their doctor.
- Talk to your doctor before you start any new medication. This includes prescription and nonprescription medicines, vitamins, and herbal supplements. XSTAN-AMH Tablets and certain other medicines can interact with each other causing serious side effects.

10. Details of Manufacturer

Pure & Cure Healthcare Pvt. Ltd.
(A subsidiary of Akums Drugs & Pharmaceuticals Ltd.),
Plot No. 26A, 27-30, Sector -8A, I.I.E., SIDCUL,
Ranipur, Harirdwar-249 403, Uttarakhand.

11. Details of Permission or License Number with Date

Mfg. Lic. No. : 31/UA/2013, Date of Product Permission: 10/05/2023.

12. Date of Revision

May 2023.

Marketed by:
EXCEL || EXCEL
Division of
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.