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 and Hydrochlorothiazide Tablets IP
(Brand Name: XSTAN®-H Tablets)

2. Qualitative and Quantitative Composition

Each Uncoated Bilayered Tablet Contains:
Telmisartan IP ……. 40 mg
Hydrochlorothiazide IP ……..… 12.5 mg
Excipients …….……. q.s.
Colours: Lake of Brilliant Blue

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Telmisartan 40 mg and Hydrochlorothiazide 12.5 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

XSTAN-H Tablets are indicated for the treatment of essential hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
XSTAN-H Tablets are usually administered in patients whose blood pressure is not adequately controlled by telmisartan monotherapy.
XSTAN-H Tablets may be used alone or in combination with other antihypertensive agents.

4.2Posology and Method of Administration

For oral administration in adults.
Usual Dose: 1 tablet of XSTAN-H 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.

If blood pressure remains uncontrolled, consider a change to more appropriate treatment.
XSTAN-H 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-H Tablets are contraindicated in the following:

- Hypersensitivity to telmisartan or to hydrochlorothiazide/sulfonamide-derived drugs or to any component of the formulation.
- In patients with anuria.
- Second and third trimesters of pregnancy.
- Severe hepatic impairment, cholestasis, and biliary obstructive disorders.
- Severe renal impairment (creatinine clearance <30 ml/min).
- Refractory hypokalaemia, hypercalcaemia, and hyponatraemia.
- The concomitant use of XSTAN-H 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.

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.

Hydrochlorothiazide

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.

4.6Use in Special Populations

Pregnant Women

Telmisartan: Pregnancy Category D; Hydrochlorothiazide: Pregnancy Category B. There are no adequate clinical data on use of telmisartan/hydrochlorothiazide combination therapy in pregnant women. Studies in animals have shown reproductive toxicity.
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.
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.
There is limited experience with hydrochlorothiazide use during pregnancy, especially during the first trimester. Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics exposes mother and fetus to unnecessary hazard.
XSTAN-H Tablets are contraindicated during the second and third trimesters of pregnancy. When pregnancy is detected or planned, treatment with XSTAN-H Tablets should be discontinued immediately and appropriate alternative therapy should be initiated.

Lactating Women
Thiazides appear in human milk. 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 during treatment with telmisartan-containing preparations. 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 effectiveness of XSTAN-H Tablets in paediatric patients have not been established. Thus, XSTAN-H Tablets are not recommended for use in children.

Geriatric Patients
No overall differences in the effectiveness and safety of telmisartan/hydrochlorothiazide were observed in elderly patients compared to younger patients. 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.
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

No dose adjustment is required in patients with mild (creatinine clearance, CrCl 60 to 90 ml/min) or moderate (CrCl 30 to 60 ml/min) renal impairment. Safety and effectiveness of XSTAN-H Tablets in patients with severe renal impairment (CrCl ≤ 30 ml/min) have not been established. Thus, XSTAN-H Tablets are contraindicated in patients with severe renal impairment.
Patients on dialysis may develop orthostatic hypotension and thus, blood pressure should be closely monitored.

Hepatic Impairment Patients
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. Minor alterations of fluid and electrolyte balance due to hydrochlorothiazide may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.
XSTAN-H Tablets (telmisartan 40mg/hydrochlorothiazide 12.5mg) should be used with caution in patients with mild to moderate hepatic impairment. In these patients, telmisartan dose should not exceed 40 mg once daily. XSTAN-H Tablets are contraindicated in patients with severe hepatic impairment or cholestasis or biliary obstructive disorders.

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. Hydrochlorothiazide can have minor or moderate influence on the ability to drive and use machines, particularly at the initiation of the therapy. When driving vehicles or operating machinery, it should be taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.

4.8Undesirable Effects
Clinical Trials Experience
Adverse events occurring at an incidence of 2% or more in patients treated with telmisartan/hydrochlorothiazide and at a greater rate than in patients treated with placebo, irrespective of their causal association, were as follows:
Body as a Whole: Fatigue, influenza-like symptoms.
Central/Peripheral Nervous System: Dizziness.
Gastrointestinal System: Diarrhea, nausea.
Respiratory System Disorder: Sinusitis, upper respiratory tract infections.

Other adverse reactions observed for telmisartan/hydrochlorothiazide were pain (including back and abdominal), dyspepsia, erythema, vomiting, bronchitis, and pharyngitis.

Telmisartan
Other adverse events that have been reported with telmisartan are listed below:
Autonomic Nervous System: Impotence, increased sweating, flushing.
Body as a Whole: Allergy, fever, leg pain, chest pain.

Cardiovascular: Palpitation, angina pectoris, abnormal ECG, hypertension, peripheral edema.
Central Nervous System: Insomnia, somnolence, migraine, paresthesia, involuntary muscle contractions, hypoesthesia.
Gastrointestinal: Flatulence, constipation, gastritis, dry mouth, hemorrhoids, gastroesophageal reflux, toothache.
Hepato-Biliary: Elevations of liver enzymes or serum bilirubin.
Metabolic: Gout, hypercholesterolemia, diabetes mellitus.
Musculoskeletal: Arthritis, arthralgia, leg cramps, myalgia.
Psychiatric: Anxiety, depression, nervousness.
Resistance Mechanism: Infection, abscess, otitis media.
Respiratory: Asthma, rhinitis, dyspnea, epistaxis.
Skin: Dermatitis, eczema, pruritus.
Urinary: Frequent micturition, cystitis.
Vascular: Cerebrovascular disorder.
Special Senses: Abnormal vision, conjunctivitis, tinnitus, earache.

Hydrochlorothiazide

Other adverse events that have been reported with hydrochlorothiazide 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: Hyperglycemia, glycosuria.
Musculoskeletal: Muscle spasm.
Nervous System/Psychiatric: Restlessness.
Renal: Interstitial nephritis.
Skin: Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis.
Special Senses: Transient blurred vision, xanthopsia.
Laboratory Tests: Increase in serum creatinine and blood urea nitrogen (BUN) levels.

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of telmisartan/hydrochlorothiazide. 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.
Blood and Lymphatic System Disorders: Eosinophilia.
Cardiac Disorders: Atrial fibrillation, congestive heart failure, myocardial infarction, tachycardia, bradycardia.
Ear and Labyrinth Disorders: Vertigo.

General Disorders and Administration Site Conditions: Asthenia, edema.
Hepato-Biliary: Abnormal hepatic function / liver disorder.
Immune System Disorders: Anaphylactic reaction.
Infections and Infestations: Urinary tract infection.
Metabolism and Nutrition Disorders: Hypoglycemia (in diabetic patients).
Musculoskeletal and Connective Tissue Disorders: Tendon pain (including tendonitis, tenosynovitis), rhabdomyolysis.
Nervous System Disorders: Syncope.
Renal and Urinary Disorders: Renal failure, renal impairment including acute renal failure.
Reproductive System and Breast Disorders: Erectile dysfunction.
Respiratory, Thoracic and Mediastinal Disorders: Coughing.
Skin and Subcutaneous Tissue Disorders: Drug eruption (toxic skin eruption mostly reported as toxicoderma, rash, and urticaria), angioedema (with fatal outcome).
Vascular Disorder: Orthostatic hypotension.
Laboratory Tests: Increase in creatinine phosphokinase (CPK).

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.

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.

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.

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.

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.

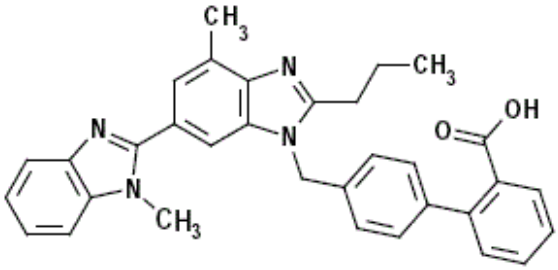
7. Description

XSTAN-H Tablets are Blue / White coloured uncoated bilayered caplet shaped tablets plain on both side.

XSTAN-H Tablets contains 40 mg of telmisartan and 12.5 mg of hydrochlorothiazide for oral administration in adults.

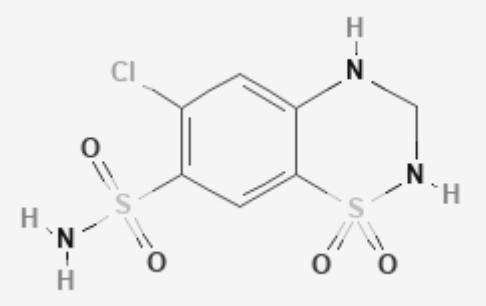
Telmisartan

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:



Inactive ingredients (excipients) of XSTAN-H Tablets contain Microcrystalline Cellulose, Colloidal Silicon Dioxide, Sodium Starch Glycolate, Sodium Hydroxide (Pellets), Meglumine, Magnesium Stearate, Lactose, Colour Brilliant Blue Lake & Polyvinyl Pyrrolidone K-30.

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 moisture at a temperature not exceeding 30°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-H 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-H 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-H 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-H Tablets if they have severe liver dysfunction or cholestasis or biliary obstructive disorders.
- Patients should be informed that while taking XSTAN-H 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-H Tablets and certain other medicines can interact with each other causing serious side effects.

10. Details of Manufacturer	**11. Details of Permission or License Number with Date**
A. Pure & Cure Healthcare Pvt. Ltd. (A subsidiary of Akums Drugs & Pharmaceuticals Ltd.) Plot No. 26A, 27-30, Sector-8A, I.I.E., SIDCUL, Haridwar – 249 403, Uttarakhand.	Mfg. Lic. No. : 31/UA/2013, Date of Product Permission: 11/05/2020
B. The Madras Pharmaceuticals, 137-B, Old Mahabalipuram Road, Karapakkam, Chennai – 600 096.	Mfg. Lic. No. : 247, Date of Product Permission : 08/02/2018

12. Date of Revision

May 2021.

Marketed by:

EXCEL BLUE CROSS || 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.