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 Tablets IP
(Brand Name: XSTAN® 20 mg / 40 mg Tablets)

2. Qualitative and Quantitative Composition

Each uncoated tablet contains:
Telmisartan IP ……..…..… 20 mg / 40 mg.
Excipients ……. q.s.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Telmisartan 20 mg / 40 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

XSTAN Tablets are indicated in the following:

- **Hypertension:** XSTAN 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.
- **Cardiovascular Risk Reduction:** XSTAN Tablets are indicated for reduction of the risk of myocardial infarction, stroke, or death from cardiovascular causes in patients 55 years of age or older at high risk of developing major cardiovascular events.

4.2Posology and Method of Administration

For oral administration in adults.

- **Hypertension:** Dosage must be individualized. The usual effective dose of telmisartan is 20 to 40 mg once a day. Blood pressure response is dose-related over the range of 20 to 80 mg. Most of the antihypertensive effect is apparent within 2 weeks and maximal reduction is generally attained after 4 weeks.

  If the target blood pressure is not achieved within 4 to 8 weeks, the dose of telmisartan can be increased to a maximum of 80 mg once daily. XSTAN Tablets may be administered with other antihypertensive drugs. When additional blood pressure reduction is required, a thiazide-type diuretic may be added.
- **Cardiovascular Risk Reduction:** The recommended dose of telmisartan is 80 mg once daily. It is not known whether doses lower than 80 mg of telmisartan are

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

XSTAN Tablets may be administered with or without food. The tablet should be swallowed whole with water.
Or, as prescribed by the physician.

4.3Contraindications

XSTAN Tablets are contraindicated in the following:

- Hypersensitivity to telmisartan or to any component of the product.
- Second and third trimesters of pregnancy.
- Severe hepatic impairment and biliary obstructive disorders.
- 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

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.

4.5Drug Interactions

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.

4.6Use in Special Populations

Pregnant Women

Pregnancy Category D. 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. Telmisartan is contraindicated during the second and third trimesters of pregnancy. When pregnancy is detected or planned, treatment with telmisartan should be discontinued immediately and appropriate alternative therapy should be initiated.

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.

Lactating Women

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. 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 telmisartan in children and adolescents below 18 years of age have not been established. Thus, XSTAN Tablets are not recommended for use in paediatric population.

Geriatric Patients
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. No dose adjustment is necessary for elderly patients.

Renal Impairment Patients
Dosage adjustment is not required for patients with mild to moderate renal impairment. A lower starting dose of 20 mg telmisartan is recommended in these patients. 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.

Hepatic Impairment Patients
As the majority of telmisartan is eliminated by biliary excretion, telmisartan is 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. Telmisartan should be used with caution in patients with mild to moderate hepatic impairment. In these patients, initiate telmisartan treatment at lower dose and up-titrate slowly; the dose should not exceed 40 mg once daily. XSTAN Tablets are contraindicated in patients with severe hepatic impairment.

4.7Effect on Ability to Drive and Use Machines
When driving vehicles or operating machinery, it should be taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy such as telmisartan.

4.8Undesirable Effects
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.

4.9Overdose

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.

5. Pharmacological Properties

5.1 Mechanism of Action

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.

5.2Pharmacodynamic Properties

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.

5.3Pharmacokinetic Properties

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.

6. Nonclinical Properties

6.1 Animal Toxicology

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).

7. Description

XSTAN 20 Tablets are White to off white uncoated circular shaped, flat beveled edge tablets with breakline on one side and plain on other side.

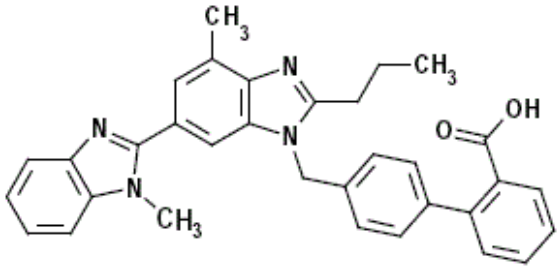
XSTAN 40 Tablets are White to off white, uncoated, oval shaped tablets plain on both sides.

XSTAN 20 Tablets contains 20 mg of telmisartan whereas XSTAN 40 Tablets contains 40 mg of telmisartan for oral administration in adults.

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:



Inactive ingredients (excipients) of XSTAN 20/XSTAN 40 Tablets contain Microcrystalline Cellulose, Colloidal Silicon Dioxide, Sodium Starch Glycolate, Sodium Hydroxide (Pellets), Meglumine & Magnesium Stearate.

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 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 Tablets once a day at any time of day at about the same time each day with or without food.
- If patients miss a dose, they can take it as soon as they remember. Do not take XSTAN 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 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 Tablets if they have severe liver dysfunction or cholestasis or biliary obstructive disorders.
- Patients should be informed that while taking XSTAN 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 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.	Xstan 20 Tablets : Mfg. Lic. No. : 31/UA/2013, Date of Product Permission:30/06/2014 Xstan 40 Tablets : Mfg. Lic. No. : 31/UA/2013, Date of Product Permission:02/07/2020
B. The Madras Pharmaceuticals, 137-B, Old Mahabalipuram Road, Karapakkam, Chennai – 600 096	Xstan 20 / Xstan 40 Tablets : Mfg. Lic. No. : 247, Date of Product Permission: 30/05/2013

12. Date of Revision

May 2021.

Marketed by:

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.