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 Metoprolol Succinate Extended Release Tablets
(Brand Name: XSTAN®-BETA 25 / 50 Tablets)

2. Qualitative and Quantitative Composition

XSTAN-BETA 25 Tablets

Each Film Coated Bilayered Tablet Contains:
Telmisartan IP ……..... 40 mg
Metoprolol Succinate IP equivalent to Metoprolol Tartrate …… 25 mg
(as extended release)
Excipients …… q.s.
Colours: Red Oxide of Iron & Titanium Dioxide IP

XSTAN-BETA 50 Tablets

Each Film Coated Bilayered Tablet Contains:
Telmisartan IP ……..... 40 mg
Metoprolol Succinate IP equivalent to Metoprolol Tartrate …… 50 mg
(as extended release)
Excipients …… q.s.
Colours:Yellow Oxide of Iron, Red Oxide of Iron & Titanium Dioxide IP

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Telmisartan 40 mg / 40 mg with Metoprolol succinate (in extended release form) 25 mg / 50 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

XSTAN-BETA Tablets are indicated for the treatment of hypertension with associated Coronary Artery Disease (CAD) or Heart Failure.

4.2Posology and Method of Administration

For oral administration in adults.
Recommended starting dose is 1 tablet of XSTAN-BETA 25 (telmisartan 40mg/metoprolol 25mg) to be administered once daily. Adjust dosage according to blood pressure goals. If blood pressure is not adequately controlled after 2 to 4 weeks of therapy, switch to higher

dosage strength i.e., 1 tablet of XSTAN-BETA 50 (telmisartan 40mg/metoprolol 50mg) to be administered once daily. If effect is optimum, continue the same dose. If blood pressure remains uncontrolled, consider a change to more appropriate treatment. 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.
- Metoprolol succinate is effective in doses between 25 to 100 mg once daily.

XSTAN-BETA Tablets should be preferably administered with or immediately following meals. 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-BETA Tablets are contraindicated in the following:

- Hypersensitivity to telmisartan or to metoprolol or to any component of the product.
- Pregnancy.
- Lactation
- 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).
- Severe bradycardia.
- Second or third degree heart block.
- Cardiogenic shock.
- Decompensated cardiac failure.
- Sick sinus syndrome (unless a permanent pacemaker is in place).

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.

Metoprolol

Abrupt Cessation of Therapy: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered metoprolol, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1 to 2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, promptly reinstate metoprolol, and take measures appropriate for the management

of unstable angina. Because coronary artery disease is common and may be unrecognized, avoid abruptly discontinuing in patients treated for hypertension.

Heart Failure: Worsening cardiac failure may occur during up-titration of metoprolol succinate. If such symptoms occur, increase diuretics and restore clinical stability before advancing the dose of metoprolol succinate. It may be necessary to lower the dose of metoprolol succinate or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of metoprolol succinate.

Bronchospastic Disease: Patients with bronchospastic diseases should, in general, not receive beta-blockers. Because of its relative beta-1 cardio-selectivity, metoprolol may be used in patients with bronchospastic disease who do not respond to, or cannot tolerate, other anti- hypertensive treatment.

Pheochromocytoma: If metoprolol succinate is used in the setting of pheochromocytoma, it should be given in combination with an alpha blocker, and only after the alpha blocker has been initiated. Administration of beta-blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta-mediated vasodilatation in skeletal muscle.

Major Surgery: Avoid initiation of a high-dose regimen of extended-release metoprolol in patients undergoing non-cardiac surgery, since such use in patients with cardiovascular risk factors has been associated with bradycardia, hypotension, stroke, and death. Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery. However, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of beta-blockade may precipitate a thyroid storm.

Diabetes and Hypoglycemia: Beta-blockers may mask tachycardia occurring with hypoglycemia.

Anaphylactic Reaction: While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine used to treat an allergic reaction.

Peripheral Vascular Disease: Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.

Calcium Channel Blockers: Because of significant inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly.

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.

Metoprolol

Catecholamine Depleting Drugs: Catecholamine-depleting drugs (e.g., reserpine, monoamine oxidase inhibitors) may have an additive effect when given with beta-blocking agents. Observe patients treated with metoprolol plus a catecholamine depletor for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

CYP 2D6 Inhibitors: Drugs that inhibit CYP 2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase metoprolol concentration.

Digitalis, Clonidine, and Calcium Channel Blockers: Digitalis glycosides, clonidine, diltiazem and verapamil slow atrioventricular conduction and decrease heart rate. Concomitant use with beta-blockers can increase the risk of bradycardia. If replacing clonidine by beta-blocker therapy, delay the introduction of beta-blockers for several days after clonidine administration has stopped.

Insulin and Oral Hypoglycemic Drugs: In diabetic patients who use insulin, beta-blocker treatment may be associated with increased or prolonged hypoglycaemia. Beta-blockers may also antagonize the hypoglycemic effects of sulfonylureas. The risk of either effect is less

with a beta-1 selective drug such as metoprolol than with a non-selective beta-blocker. However, diabetic patients receiving metoprolol should be monitored to ensure that diabetes control is maintained.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Concurrent treatment with NSAIDs such as indomethacin may decrease the antihypertensive effect of metoprolol.

4.6Use in Special Populations

Pregnant Women

Telmisartan: Pregnancy Category D; Metoprolol Succinate: 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.

Metoprolol has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 22 times, on a mg/m² basis. When metoprolol tartrate is administered to the pregnant animal (mice), fetus gets exposed with the drug. Animal studies have revealed no evidence of impaired fertility or teratogenicity.

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-BETA Tablets are contraindicated during the second and third trimesters of pregnancy. When pregnancy is detected or planned, treatment should be discontinued immediately and appropriate alternative therapy should be initiated.

Lactating Women

Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the metoprolol. 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 XSTAN-BETA Tablets. Accordingly, a decision should be made whether to discontinue nursing or discontinue the therapy, taking into account the importance of these drugs to the mother.

Paediatric Patients

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

Geriatric Patients

With telmisartan and metoprolol, 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. In general, a lower initial starting dose is recommended in elderly patients given their greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease and/or other drug therapy. Dosage up-titration, if required, should be done with caution.

Renal Impairment Patients

The bioavailability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Telmisartan can be administered in patients with mild to moderate renal dysfunction. With telmisartan, there is limited experience in patients with severe renal impairment or hemodialysis. Patients on dialysis may develop orthostatic hypotension and thus, blood pressure should be closely monitored.

Dosage adjustment of XSTAN-BETA Tablets is not required for patients with mild to moderate renal impairment. Due to lack of safety data, XSTAN-BETA Tablets are not recommended in patients with severe renal impairment.

Hepatic Impairment Patients

As metoprolol is metabolized by the liver, metoprolol blood levels are likely to increase substantially with poor hepatic function. Thus, in patients with impaired hepatic function, initiate therapy with lower doses and if required, increase doses gradually.

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. XSTAN-BETA Tablets 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-BETA Tablets are contraindicated in patients with severe hepatic impairment.

4.7Effect on Ability to Drive and Use Machines

As with all beta-blockers, metoprolol may affect patients' ability to drive and operate machinery. It should be taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy. If affected, patients should avoid driving or operating machinery or engaging in other tasks that require mental alertness.

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.

Metoprolol
The following adverse reactions have been reported with use of metoprolol:

- Worsening angina or myocardial infarction.
- Worsening heart failure.
- Worsening AV block.

Clinical Trials Experience

Most adverse reactions have been mild and transient. The most commonly (>2%) reported adverse reactions are tiredness, accident and/or injury, dizziness, vertigo, depression, diarrhea, shortness of breath, bradycardia, and rash.

Post-Marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular: Cold extremities, arterial insufficiency (usually of the Raynaud type), palpitations, peripheral edema, syncope, chest pain, and hypotension.

Respiratory: Wheezing (bronchospasm), dyspnea.

Central Nervous System: Confusion, short-term memory loss, headache, somnolence, nightmares, insomnia, anxiety/nervousness, hallucinations, paresthesia.

Gastrointestinal: Nausea, dry mouth, constipation, flatulence, heartburn, hepatitis, vomiting.

Hypersensitive Reactions: Pruritus.

Miscellaneous: Musculoskeletal pain, arthralgia, blurred vision, decreased libido, male impotence, tinnitus, reversible alopecia, agranulocytosis, dry eyes, worsening of psoriasis, sweating, photosensitivity, taste disturbance.

Laboratory Tests: Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

4.9Overdose

Telmisartan

Symptoms: 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.

Treatment: 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.

Metoprolol

Symptoms: Overdose of metoprolol may lead to severe bradycardia, hypotension, and cardiogenic shock. Clinical presentation can also include atrioventricular block, heart failure, bronchospasm, hypoxia, impairment of consciousness/coma, nausea and vomiting.

Treatment: Consider treating the patient with intensive care. Patients with myocardial infarction or heart failure may be prone to significant hemodynamic instability. There is very

limited experience with the use of hemodialysis to remove metoprolol, however, metoprolol is not highly protein bound.
If any of the following conditions occur, general treatment should include:

- **Bradycardia:** Administer intravenous atropine; repeat the dose if efficacy is adequate. If the response is inadequate, consider intravenous isoproterenol or other positive chronotropic agents. Evaluate the need for transvenous pacemaker insertion.
- **Hypotension:** Treat underlying bradycardia. Consider intravenous vasopressor infusion, such as dopamine or norepinephrine.
- **Bronchospasm:** Can usually be reversed by bronchodilators. Administer a beta-2 agonist, including albuterol inhalation, or an oral theophylline derivative.
- **Heart Failure and Shock:** May be treated with suitable volume expansion, injection/infusion of glucagon, intravenous administration of adrenergic drugs such as dobutamine, with alpha-1 receptor agonistic drugs added in presence of vasodilation.

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.

Metoprolol

Metoprolol is a selective β_1 receptor blocking drug. Proposed mechanisms by which metoprolol produces antihypertensive effect are as follow:

1) Competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output.
2) Central effect leading to reduced sympathetic outflow to the periphery.
3) Suppression of renin activity.

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.

Metoprolol

Metoprolol is a beta-1 selective (cardioselective) adrenergic receptor blocking agent. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.
Beta-blocking action of metoprolol leads to following effects:

1. Reduction in heart rate and cardiac output at rest and upon exercise.
2. Reduction of systolic blood pressure upon exercise.
3. Inhibition of isoproterenol-induced tachycardia.
4. Reduction of reflex orthostatic tachycardia.

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.

Metoprolol

Absorption: Absorption of metoprolol is rapid and complete. Bioavailability after oral administration of conventional metoprolol is 50%, indicating about 50% first-pass metabolism.
Distribution: Metoprolol crosses the blood-brain barrier and has been reported in the cerebrospinal fluid (CSF). Plasma levels achieved are highly variable after oral

administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin.

Metabolism: Metoprolol is a racemic mixture of R- and S-enantiomers, and is primarily metabolized by CYP 2D6. When administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype.

Excretion: Excretion is mainly by biotransformation in the liver, and the plasma half-life ranges from 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity.

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).

Metoprolol

Carcinogenesis: Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day (41 times, on a mg/m² basis, the daily dose of 200 mg for a 60-kg patient), there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia.
In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day (18 times, on a mg/m² basis, the daily dose of 200 mg for a 60-kg patient), benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.
Mutagenesis: All genotoxicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a Salmonella/mammalian-microsome mutagenicity test) were negative.
Impairment of Fertility: No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 22 times, on a mg/m² basis, the daily dose of 200 mg in a 60-kg patient.
Teratogenicity: Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 22 times, on a mg/m² basis, the daily dose of 200 mg in a 60-kg patient. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity.

7. Description

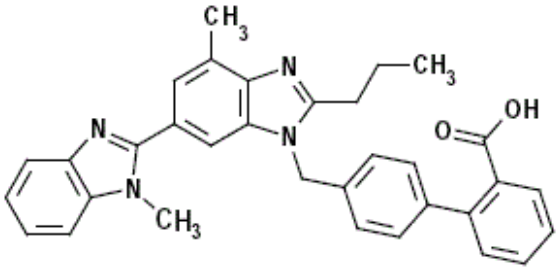
XSTAN-BETA 25 Tablets are Brown coloured, round, biconvex, film coated extended release bilayered tablets plain on both sides.

XSTAN-BETA 50 Tablets are Brown coloured, round, biconvex, film coated extended release bilayered tablets plain on both sides.

XSTAN-BETA 25 Tablets contains 40 mg of telmisartan and 25 mg of metoprolol succinate (in extended release form) for oral administration in adults.
XSTAN-BETA 50 Tablets contains 40 mg of telmisartan and 50 mg of metoprolol succinate (in extended release form) for oral administration in adults.

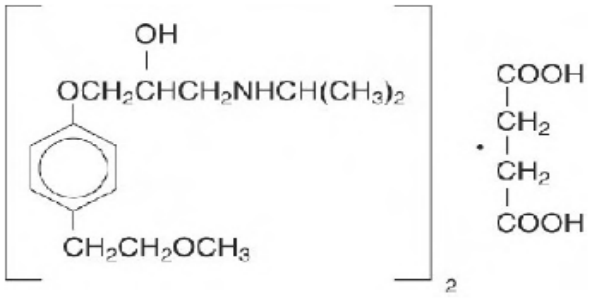
Telmisartan

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:



Metoprolol Succinate

Metoprolol succinate is a cardioselective adrenoceptor blocking agent having antihypertensive properties. Metoprolol succinate (extended release form) is the succinate salt form of metoprolol.
Metoprolol succinate is a white crystalline powder. It is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl-acetate, acetone, diethylether and heptane.
Molecular Weight: 652.8 g/mol.
Molecular Formula: C34H56N2O10.
Chemical Name: (±)1- (isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt).
Structural Formula:



Inactive ingredients (excipients) of XSTAN-BETA 25 Tablets contain Hydroxyl Propyl Cellulose, Microcrystaline Cellulose, Sodium Lauryl Sulphate, Polysorbate 80, Pregelatinised Starch, Colour Iron Oxide of Red, Magnesium Stearate, Colloidal Silicon Dioxide, Sodium Starch Glycolate, Crosspovidone, Methocel K100M, Ethyl cellulose, Isopropyl Alcohol, Methylene Chloride, Colloidal silicon Dioxide, Sodium Stearyl Fumerate & Talcum.

Inactive ingredients (excipients) of XSTAN-BETA 50 Tablets contain Hydroxyl Propyl Cellulose, Microcrystaline Cellulose, Sodium Lauryl Sulphate, Polysorbate 80, Pregelatinised Starch, Colour Iron Oxide of Red, Colour Iron Oxide of Yellow, Magnesium Stearate, Colloidal Silicon Dioxide, Sodium Starch Glycolate, Crosspovidone, Methocel K100M, Ethyl cellulose, Isopropyl Alcohol, Methylene Chloride, Colloidal silicon Dioxide, Sodium Stearyl Fumerate, Talcum, Hydroxy propyl methyl cellulose, Polyethylene glycol 6000 & Titanium Dioxide.

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 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-BETA Tablets once a day at any time of day at about the same time each day. Advise patients to take this medicine, preferably with or immediately following meals. Do not cut, crush or chew the tablet.
- If patients miss a dose, they can take it as soon as they remember. Do not take XSTAN-BETA 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-BETA 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-BETA Tablets if they have severe liver dysfunction or cholestasis or biliary obstructive disorders.
- If any difficulty in breathing occurs, patients to contact their physician immediately.
- Heart failure patients should be advised to consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath.
- Patients should be informed that while taking XSTAN-BETA 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-BETA Tablets and certain other medicines can interact with each other causing serious side effects.

10. Details of Manufacturer

Akums Drugs & Pharmaceuticals Ltd.
19, 20, 21, Sector - 6A, I.I.E., SIDCUL, Ranipur,
Haridwar - 249 403, Uttarakhand.

11. Details of Permission or License Number with Date

Mfg. Lic. No. : 10/UA/2004, Date of Product Permission: 04/01/2018

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.