*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 Amlodipine Tablets IP
(Brand Name: XSTAN®-AM Tablets)

## 2. Qualitative and Quantitative Composition

Each Uncoated Bilayered Tablet Contains:
Telmisartan IP ……..… 40 mg
Amlodipine Besylate IP equivalent to Amlodipine ……. 5 mg
Excipients …… q.s.
Colours: Lake of Ponceau 4R
(In Amlodipine Besylate Layer )

## 3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Telmisartan 40 mg with Amlodipine 5 mg per tablet.

## 4. Clinical Particulars

### 4.1 Therapeutic Indication

XSTAN-AM Tablets are indicated for the treatment of essential hypertension in adults, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
XSTAN-AM Tablets are usually administered in patients whose blood pressure is not adequately controlled by monotherapy of either telmisartan or amlodipine.
XSTAN-AM 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-AM 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.
- Amlodipine is effective over the range of 2.5 mg to 10 mg once daily.

If blood pressure remains uncontrolled, consider a change to more appropriate treatment.

XSTAN-AM 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-AM Tablets are contraindicated in the following:

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

## 4.4Special Warnings and Precautions for Use

**Telmisartan**

**Fetal Toxicity:** Use of drugs that act on the renin angiotensin aldosterone system (RAAS) during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. Thus, when pregnancy is detected, discontinue telmisartan as soon as possible.

**Hypotension:** In patients with an activated RAAS, such as volume-or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with telmisartan. Either correct this condition prior to administration of telmisartan, or start treatment under close medical supervision with a reduced dose.

**Hyperkalemia:** Hyperkalemia may occur in patients on angiotensin receptor blockers/antagonists (ARBs), particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk.

**Renovascular Hypertension:** There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with drugs that affect the RAAS.

**Dual Blockade of the RAAS:** There is evidence that the concomitant use of angiotensin-converting enzyme (ACE) inhibitors, ARBs or aliskiren increases the risk of hypotension, hyperkalemia, and decreased renal function (including acute renal failure). Dual blockade of RAAS through combined use of ACE-inhibitors, ARBs or aliskiren is therefore not

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

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

**Primary Aldosteronism:** Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the RAAS. Therefore, use of telmisartan is not recommended.

**Aortic and Mitral Valve Stenosis, Obstructive Hypertrophic Cardiomyopathy:** As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

**Diabetic Patients Treated with Insulin or Antidiabetic Drugs:** Hypoglycaemia may occur when telmisartan is co-administered with these drugs. Therefore, in these patients appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated.

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

**Amlodipine**

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

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

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

## 4.5Drug Interactions

**Telmisartan**

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

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

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

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

**Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 (Cox-2) Inhibitors:** In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ARBs, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving telmisartan and NSAID therapy. The antihypertensive effect of ARBs (including telmisartan) may be attenuated by NSAIDs, including selective COX-2 inhibitors.

**Potassium Sparing Diuretics or Potassium Supplements:** Telmisartan attenuates diuretic-induced potassium loss. Potassium sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

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

**Amlodipine**

**1) Impact of Other Drugs on Amlodipine**

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

**CYP3A Inhibitors (e.g., Ketoconazole, Itraconazole, Diltiazem, Erythromycin, Fluconazole, etc.):** Co-administration with CYP3A inhibitors results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A inhibitors to determine the need for dose adjustment.

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

**2) Impact of Amlodipine on Other Drugs**

**Simvastatin:** Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

**Immunosuppressants:** Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of blood levels of cyclosporine and tacrolimus and dosage adjustment (whenever appropriate) is recommended.

## 4.6Use in Special Populations

**Pregnant Women**

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

Hypertension in pregnancy increases the 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.

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses.

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

**Lactating Women**

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

**Paediatric Patients**

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

**Geriatric Patients**

With telmisartan, no overall differences in effectiveness and safety were observed in elderly patients compared to younger patients, but greater sensitivity of some older individuals

cannot be ruled out. Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC; therefore, caution should be exercised.
Elderly patients with normal hepatic and renal function may be given the same dose as recommended for adults.

**Renal Impairment Patients**
The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Dosage adjustment is not required for patients with mild to moderate renal impairment. Limited experience is available in patients with severe renal impairment or hemodialysis. Patients on dialysis may develop orthostatic hypotension and thus, blood pressure should be closely monitored. Due to lack of safety data, XSTAN-AM Tablets are not recommended in patients with severe renal impairment.

**Hepatic Impairment Patients**
Amlodipine is extensively metabolized by the liver and the plasma elimination half-life increases in patients with impaired hepatic function. As the majority of telmisartan is eliminated by biliary excretion, telmisartan-containing preparations are not to be given to patients with cholestasis or biliary obstructive disorders or severe hepatic insufficiency. These patients can be expected to have reduced hepatic clearance for telmisartan. XSTAN-AM 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-AM Tablets are contraindicated in patients with severe hepatic impairment.

## 4.7Effect on Ability to Drive and Use Machines
Dizziness, drowsiness headache, fatigue, or nausea may occasionally occur in patients taking antihypertensive therapy (such as amlodipine or telmisartan) which may impair patient's ability to react. Amlodipine can have minor or moderate influence on the ability to drive and use machines, particularly at the initiation of the therapy. Thus, caution is recommended while driving a vehicle or operating machinery.

## 4.8Undesirable Effects
**Telmisartan**
**Clinical Trials Experience**
Adverse events occurred at an incidence of ≥ 1% in patients treated with telmisartan and at a greater rate than in patients treated with placebo were upper respiratory tract infections (URTIs), sinusitis, pharyngitis, back pain, and diarrhea.
In addition, the adverse events occurred at a rate of ≥ 1%, but at least as frequent in the placebo group were influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea, and peripheral edema. The incidence of adverse reactions was not dose-related and showed no correlation with gender, age or race of the patients.

Adverse events that occurred in more than 0.3% patients treated with telmisartan monotherapy in controlled or open trials are as follows. It cannot be determined whether these events were causally related to telmisartan therapy.
Autonomic Nervous System: Impotence, increased sweating, flushing.
Body as a Whole: Allergy, fever, leg pain, malaise.
Cardiovascular: Palpitation, edema, angina pectoris, tachycardia, abnormal ECG.
Central Nervous System: Insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia.
Gastrointestinal: Flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, gastroesophageal reflux, nonspecific gastrointestinal disorders, toothache.
Metabolic: Gout, hypercholesterolemia, diabetes mellitus.
Musculoskeletal: Arthritis, arthralgia, leg cramps.
Psychiatric: Anxiety, depression, nervousness.
Infections: Fungal infection, abscess, otitis media.
Respiratory: Asthma, bronchitis, rhinitis, dyspnea, epistaxis.
Skin: Dermatitis, rash, eczema, pruritus.
Urinary: Increased micturition frequency, cystitis.
Vascular: Cerebrovascular disorder.
Special Senses: Abnormal vision, conjunctivitis, tinnitus, earache.
Laboratory Tests: Decrease in hemoglobin, increase in creatinine, elevations of liver enzymes may occur in patients treated with telmisartan.

**Post-Marketing Experience**
The most frequent spontaneously reported events included headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, angioneurotic edema, urticaria, hypersensitivity, increased sweating, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, increased blood pressure, aggravated hypertension, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, increased uric acid, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, increased creatine phosphokinase (CPK), anaphylactic reaction, tendon pain (including tendonitis, tenosynovitis), drug eruption (mostly reported as toxicoderma, rash, and urticaria), hypoglycemia (in diabetic patients), and angioedema (with fatal outcome). Rare cases of rhabdomyolysis have been reported in patients receiving ARBs, including telmisartan.

**Amlodipine**
Most common adverse reactions reported with amlodipine are headache and pedal edema. Adverse effects with an incidence >1% in clinical studies included abdominal pain, nausea, dizziness, somnolence, flushing, palpitations, and fatigue.
Rare adverse events observed in controlled clinical trials or open trials or post-marketing surveillance studies (causal relationship is uncertain) included:
Autonomic Nervous System: Dry mouth, increased sweating, cold and clammy skin.

Cardiovascular: Arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural hypotension, vasculitis, cardiac failure, pulse irregularity, extrasystoles.
Central and Peripheral Nervous System: Hypoesthesia, peripheral neuropathy, paresthesia, tremor, vertigo, ataxia, hypertonia, migraine, apathy, agitation, amnesia.
Gastrointestinal: Anorexia, constipation, dysphagia, diarrhea, flatulence, gastritis, increased appetite, loose stools, pancreatitis, vomiting, gingival hyperplasia/hypertrophy.
General: Allergic reaction, back pain, hot flushes, malaise, pain, rigors, weight gain, weight loss.
Hemopoietic: Leukopenia, purpura, thrombocytopenia.
Metabolic and Nutritional: Hyperglycemia, thirst.
Musculoskeletal System: Arthralgia, arthrosis, muscle cramps, myalgia, muscle weakness, twitching.
Psychiatric: Sexual dysfunction, insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.
Respiratory System: Dyspnea, epistaxis, cough, rhinitis.
Skin and Appendages: Rash, pruritus, urticaria, angioedema, skin dryness, alopecia, skin discoloration.
Special Senses: Abnormal vision, conjunctivitis, diplopia, eye pain, abnormal visual accommodation, xerophthalmia, tinnitus, parosmia, taste perversion.
Urinary System: Increased micturition frequency, nocturia, dysuria, polyuria.

## 4.9Overdose

**Telmisartan**

Limited data are available with regard to overdose in humans. The most likely manifestation of overdose with telmisartan would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation.
If symptomatic hypotension occurs, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis. Management of overdose depends on the time since ingestion and the severity of symptoms. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacement given quickly.

**Amlodipine**

Overdose may cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdose of amlodipine is limited.
If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of

vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

# 5. Pharmacological Properties

## 5.1 Mechanism of Action

**Telmisartan**

Telmisartan is a selective $AT_1$ subtype angiotensin II receptor antagonist. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin aldosterone system (RAAS), with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the $AT_1$ receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an $AT_2$ receptor found in many tissues, but $AT_2$ is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the $AT_1$ receptor than for the $AT_2$ receptor.

**Amlodipine**

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

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

## 5.2Pharmacodynamic Properties

**Telmisartan**

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

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

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

**Amlodipine**

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

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.
With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with intensity of elevated blood pressure at baseline (prior to treatment).
Thus, individuals with moderate hypertension (diastolic pressure 105 to 114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90 to 104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg).

## 5.3Pharmacokinetic Properties

**Telmisartan**

The pharmacokinetics of orally administered telmisartan is nonlinear over the dose range 20 to 160 mg, with greater than proportional increases of plasma concentrations ($C_{max}$ and AUC) with increasing doses.
**Absorption:** Following oral administration, peak plasma concentration ($C_{max}$) of telmisartan is reached in 0.5 to 1 hour after dosing. Food slightly reduces the bioavailability of telmisartan. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg, the bioavailability was 42% and 58%, respectively.
**Distribution:** Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and $\alpha_1$-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.

**Amlodipine**

**Absorption:** After oral administration of therapeutic doses, amlodipine produces peak plasma concentrations between 6 to 12 hours. Absolute bioavailability has been estimated to be between 64 to 90%. The bioavailability is not altered by the presence of food.
**Distribution:** The volume of distribution is approximately 21 l/kg. *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.
**Metabolism:** Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.

**Excretion:** Excretion from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

# 6. Nonclinical Properties

## 6.1 Animal Toxicology

**Telmisartan**

Carcinogenicity: There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a $mg/m^2$ basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of telmisartan. These same doses have been shown to provide average systemic exposures to telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD of telmisartan (80 mg/day).

Mutagenesis: Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella and E. coli (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test.

Impairment of Fertility: No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a $mg/m^2$ basis, the MRHD of telmisartan. This dose in the rat resulted in an average systemic exposure (telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day).

Teratogenicity: No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses of up to 45 mg/kg/day. In rabbits, embryo lethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day (approximately 12 times the maximum recommended human dose [MRHD] of 80 mg on a $mg/m^2$ basis). In rats, maternally toxic (reduced body weight gain and food consumption) telmisartan doses of 15 mg/kg/day (approximately 1.9 times the MRHD on a $mg/m^2$ basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. The no-observed effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are approximately 0.64 and 3.7 times, respectively, on a $mg/m^2$ basis, the MRHD of telmisartan (80 mg/day).

**Amlodipine**

Carcinogenesis: Rats and mice treated with amlodipine in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 amlodipine mg/kg/day, showed no evidence of a carcinogenic effect of the drug.

Mutagenesis: Mutagenicity studies conducted with amlodipine revealed no drug related effects at either the gene or chromosome level.

Impairment of Fertility: There was no effect on the fertility of rats treated orally with amlodipine (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times [based on body weight of 50 kg] the maximum recommended human dose of 10 mg/day on a mg/$m^2$ basis).
Teratogenicity: No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine at doses up to 10 mg amlodipine/kg/day (approximately 10 and 20 times the maximum recommended human dose based on body surface area, respectively) during their respective periods of major organogenesis. However for rats, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

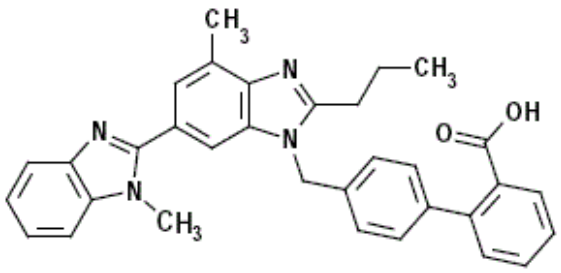
## 7. Description

XSTAN-AM Tablets are Pink & white to off white coloured, elongated, biconvex, both side plain & uncoated bi-layered Tablets.

XSTAN-AM Tablets contains 40 mg of telmisartan and 5 mg of amlodipine for oral administration in adults.

**Telmisartan**

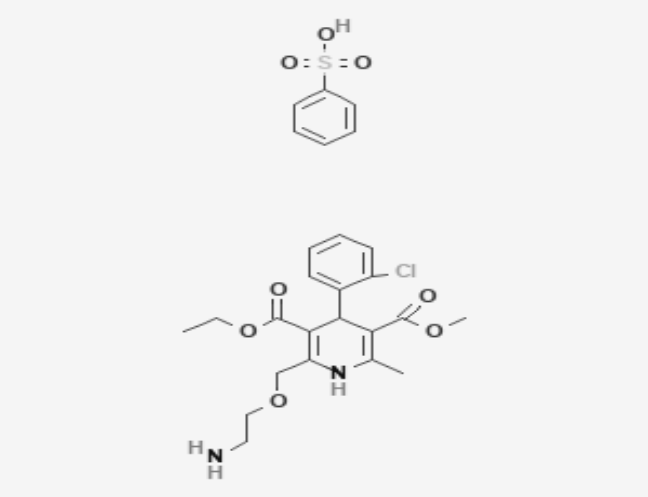
Telmisartan is an angiotensin II receptor ($AT_1$) antagonist class of antihypertensive agent. Telmisartan is a white to slightly yellowish solid. It is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid, and soluble in strong base.
Molecular Weight: 514.63 g/mol.
Molecular Formula: C33H30N4O2.
Chemical Name: 4'-[(1,4'-dimethyl-2'-propyl [2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid.
Structural Formula:




**Amlodipine Besylate**

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

Molecular Weight: 567.1 g/mol.
Molecular Formula: C20H25CIN2O5•C6H6O3S.
Chemical Name: 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(2- chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate.
Structural Formula:



Inactive ingredients (excipients) of XSTAN-AM Tablets contain Di-basic calcium phosphate, Microcrystalline Cellulose, Sodium Starch Glycolate, Colour Ponceau 4R Lake, Polyvinyl Pyrrolidone K-30, Isopropyl Alcohol, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxy Propyl Cellulose, Lactose, Sodium Hydroxide (Pellets), Sorbimine-A, Polysorbate 80, Aerocal-C & Crospovidone INF 10.

## 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-AM 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-AM 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-AM 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-AM Tablets if they have severe liver dysfunction or cholestasis or biliary obstructive disorders.
- Patients should be informed that while taking XSTAN-AM 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-AM Tablets and certain other medicines can interact with each other causing serious side effects.

## 10. Details of Manufacturer

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

## 11. Details of Permission or License Number with Date

Mfg. Lic. No. : 31/UA/2013, Date of Product Permission: 09/02/2018

## 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.

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