Biocon

℞

Telmisartan 40mg and Amlodipine 5mg Tablets IP

TELMISAT - AM® 5

टेलमिसेट - ए एम ५

COMPOSITION
Each uncoated bilayered tablet contains :
Telmisartan IP 40 mg
Amlodipine Besilate IP
Eq.to Amlodipine 5 mg
Excipients q.s.
Colour: Ferric Oxide USP- NF Yellow

WARNING
AVOID USE IN PREGNANCY
When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Telmisartan tablets should be discontinued as soon as possible.

Special Alerts:
ISSUE: A recently published study a meta-analysis combining cancer related findings from several clinical trials suggested use of angiotensin receptor blockers (ARBs) may be associated with a little increased risk of cancer

RECOMMENDATION: FDA has not concluded that ARBs increase the risk of cancer. The Agency is reviewing information related to this safety concern and will update the public when additional information is available. FDA believes the benefits of ARBs continue to outweigh their potential risks. For more information visit the FDA website.

PHARMACEUTICAL FORM
Tablets
PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group: Angiotensin II Antagonist and Calcium channel blocker .
ATC code: C09DB04

Description:
Telmisartan:
Telmisartan is a non-peptide Angiotensin I receptor (AT1) antagonist.
Telmisartan is chemically described as 4'-[(1,4'-dimethyl-2'-propyl [2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid. Its empirical formula is $C_{33}H_{30}N_4O_2$, its molecular weight is 514.63.
Telmisartan is hygroscopic and require protection from moisture.

Amlodipine:
Amlodipine Besilate is the Besilate salt of Amlodipine, a long-acting calcium channel blocker.
Amlodipine besilate is chemically described as 3-Ethyl-5-methyl(±)-2-[(2aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate mono benzenesulphonate. Its molecular formula is $C_{20}H_{25}ClN_2O_5C_6H_6O_3S$.

Clinical pharmacology:
Telmisartan:
Mechanism of Action
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 system, 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 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.

Pharmacokinetics
Absorption:
Following oral administration, peak concentrations (C_{max}) of telmisartan attained in 0.5-1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are about 10-25% of peak plasma concentrations.

Distribution
Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and α1 - acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 liters indicating additional tissue binding.

Metabolism and Elimination
Telmisartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma.

Following oral administration of ^{14}C-labeled telmisartan, most of the administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively). Total plasma clearance of telmisartan is >800 mL/min.

Special Populations
Pediatric : Telmisartan pharmacokinetics have not been investigated in patients <18 years of age.
Geriatric : The pharmacokinetics of telmisartan does not differ between the elderly and those younger than 65 years.
Gender : Plasma concentrations of telmisartan are generally 2-3 times higher in females than in males. In clinical trials, however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary.
Renal Insufficiency : No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by haemofiltration.
Hepatic Insufficiency : In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100%.

AMLODIPINE:
Mechanism of Action:
Amlodipine is a dihydropyridine calcium channel blocker, which inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. 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. 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.

Pharmacokinetics:
Absorption:
After oral administration of Amlodipine, a peak plasma concentration is achieved between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 % to 90%. The bioavailability of Amlodipine is not altered by the presence of food.

Distribution and 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.

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

Renal insufficiency:
The pharmacokinetics of Amlodipine is not significantly influenced by renal impairment. Patients with renal failure may therefore can take the usual initial dose.

Geriatric and Hepatic insufficiency:
Elderly patients and patients with hepatic insufficiency have decreased clearance of Amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose may be required

Pediatric Patients:
Sixty-two hypertensive patients aged 6 to 17 years received doses of Amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

Indication:
Indicated for the treatment of hypertension.

Dosage and administration:
The recommended dosage is one tablet administered once daily with or without food. It can be coadministred with other antihypertensive agents as per the direction of the physician.

Contraindication:
Telmisartan and Amlodipine tablets are contraindicated in patients who are hypersensitive to any component of this product, and also in
1. Patients suffering from Anuria.
2. Pregnant and lactating females.
3. Hereditary or idiopathic angioedema.

Warnings and precautions:
Telmisartan:

General
Impaired Hepatic Function: As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Telmisartan tablets should be used with caution in these patients.

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with Telmisartan tablets.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of Telmisartan tablets in patients with unilateral or bilateral renal artery stenosis but an effect similar to that seen with ACE inhibitors should be anticipated.

Fetal/Neonatal Morbidity and Mortality
Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, Telmisartan tablets should be discontinued as soon as possible.

Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development.

Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

If oligohydramnios is observed, Telmisartan tablets should be discontinued unless they are considered lifesaving for the mother. Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia.

Hypotension in Volume-Depleted Patients
In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with Telmisartan tablets. This condition should be corrected prior to administration of Telmisartan tablets, or treatment should start under close medical supervision with a reduced dose.

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

Biocon

℞

Telmisartan 40mg and Amlodipine 5mg Tablets IP

TELMISAT - AM® 5

टेलमिसेट - ए एम ५

Amlodipine:
WARNINGS
Increased Angina and/or Myocardial Infarction:
Rarely, patients with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

PRECAUTIONS
General: Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution, as with any other peripheral vasodilator, should be exercised when administering Amlodipine besilate Tablets, particularly in patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure: In general, calcium channel blockers should be used with caution in patients with heart failure.

Patients with Hepatic Failure: Since amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering Amlodipine Besilate Tablets to patients with severe hepatic impairment.

Adverse reactions:
Telmisartan:
Telmisartan tablets have been evaluated for safety in more than 3700 patients, including 1900 treated for over six months and more than 1300 for over one year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

In placebo-controlled trials involving 1041 patients treated with various doses of telmisartan (20-160 mg) monotherapy for up to 12 weeks, an overall incidence of adverse events similar to that of placebo was observed. The adverse events being Upper respiratory tract infections, Back pain, Sinusitis, Diarrhea and Pharyngitis.

The following events occurred at a rate of 1% but were at least as frequent in the placebo group: 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 events was not dose-related and did not correlate with gender, age, or race of patients. The incidence of cough occurring with telmisartan in six placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%). In addition to those listed above, adverse events that occurred in more than 0.3% of 3500 patients treated with Telmisartan tablets monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to Telmisartan tablets: Autonomic Nervous System: impotence, increased sweating, flushing; Body as a Whole: allergy, fever, leg pain, malaise; Cardiovascular: palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG; CNS: insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoaesthesia; Gastrointestinal: flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders; Metabolic: gout, hypercholesterolemia, diabetes mellitus; Musculoskeletal: arthritis, arthralgia, leg cramps; Psychiatric: anxiety, depression, nervousness; Resistance Mechanism: infection, fungal infection, abscess, otitis media; Respiratory: asthma, bronchitis, rhinitis, dyspnea, epistaxis; Skin: dermatitis, rash, eczema, pruritus; Urinary: micturition frequency, cystitis; Vascular: cerebrovascular disorder; and Special Senses: abnormal vision, conjunctivitis, tinnitus, earache.

Clinical Laboratory Findings
In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of Telmisartan tablets.

Hemoglobin: A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy due to anemia.

Creatinine: A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.

Liver Enzymes: Occasional elevations of liver chemistries occurred in patients treated with Telmisartan; all marked elevations occurred at a higher frequency with placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

Cardiovascular Risk Reduction Trials
In clinical studies with patients at high risk of developing major cardiovascular events, cases of sepsis, including some with fatal outcomes, have been reported.

Post-Marketing Experience
The following adverse reactions have been identified during post-approval use of Telmisartan tablets. The most frequently spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, 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, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, increased CPK, anaphylactic reaction, and tendon pain (including tendonitis, tenosynovitis). Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including Telmisartan tablets.

Amlodipine:
Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with amlodipine was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner is as follows:

Adverse Event	2.5 mg N=275	5 mg N=296	10 mg N=268	Placedo N=520
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitation	0.7	1.4	4.5	0.6

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials were headache, fatigue, nausea, abdominal pain and somnolence.
The following events occurred in <1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship.
Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.

OVERDOSAGE:
Telmisartan:
Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage with Telmisartan tablets would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis

Amlodipine:
In humans, experience with intentional overdosage of Amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted. If massive overdose should occur, active cardiac and respiratory monitoring should be instituted.

Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Presentation
TELMISAT - AM® 5 tablets are available in strip pack of 10 tablets.

Shelf life: Please refer carton/strip.

Storage: Store protected from light & moisture at a temperature not exceeding 30°C.
Keep out of reach of children.

BF/LI/37520/01

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

® - Registered trademark

Leaflet revised **August 2019**

To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free No.: **1800 102 9465** or e mail us at **drugsafety@biocon.com**