Tasmi®-AM

[Amlodipine+Telmisartan]

ٹیسمی-اے ایم

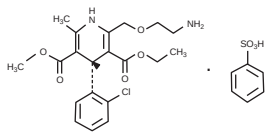
Tablets

5mg+40mg, 5mg+80mg, 10mg+40mg and 10mg+80mg

DESCRIPTION

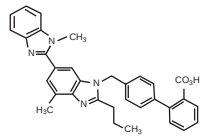
Tasmi-AM (Amlodipine + Telmisartan) is a fixed dose combination of Amlodipine and Telmisartan.

Amlodipine contains the besylate salt of amlodipine, a dihydropyridine calcium-channel blocker (CCB). Chemically, Amlodipine besylate is described as 3-Ethyl-5- methyl (4RS)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1, 4-dihydropyridine-3,5-dicarboxylate benzenesulphonate. The molecular formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ and the structural formula is:



Amlodipine Besylate

Telmisartan is a non-peptide angiotensin II receptor (type AT_1) antagonist. Its chemical name is 4'-[[4-Methyl-6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1- yl] methyl]biphenyl-2-carboxylic acid. The molecular formula is $C_{33}H_{30}N_4O_2$ and the structural formula is:



Telmisartan

QUALITATIVE & QUANTITATIVE COMPOSITION

Tasmi-AM (Amlodipine + Telmisartan) is available for oral administration as:

1. Tasmi-AM Tablets 5mg + 40mg
   Each tablet contains:
   Amlodipine … 5mg
   (as amlodipine besylate USP)
   Telmisartan USP… 40mg

2. Tasmi-AM Tablets 5mg + 80mg
   Each tablet contains:
   Amlodipine … 5mg
   (as amlodipine besylate USP)
   Telmisartan USP… 80mg

3. Tasmi-AM Tablets 10mg + 40mg
   Each tablet contains:
   Amlodipine … 10mg
   (as amlodipine besylate USP)
   Telmisartan USP... 40mg

4. Tasmi-AM Tablets 10mg + 80mg
   Each tablet contains:
   Amlodipine … 10mg
   (as amlodipine besylate USP)
   Telmisartan USP... 80mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Amlodipine

Amlodipine inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. It 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.

Telmisartan

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.

Pharmacokinetics

The pharmacokinetics of amlodipine and telmisartan when combined are similar to the pharmacokinetics of amlodipine and telmisartan when administered separately.

Amlodipine

Absorption

Amlodipine is well absorbed and the peak plasma concentrations are reached in 6 to12 hours after oral administration of amlodipine alone. Absolute bioavailability is between 64% and 80%. Amlodipine bioavailability is not altered by the presence of food.

Distribution

The apparent volume of distribution of amlodipine is approximately 21L/kg. Approximately 97.5% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

Metabolism

Amlodipine is extensively (approximately 90%) metabolized in to inactive metabolites via hepatic metabolism.

Excretion

Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after 7 to 8 days of consecutive daily dosing. 10% of the parent compound and 60% of amlodipine metabolites are excreted in urine.

Telmisartan

Absorption

Following oral administration, telmisartan is rapidly absorbed from gastro-intestinal tract. The peak plasma concentrations (C_{max}) of telmisartan are 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 40mg and 160mg the bioavailabilty is 42% and 58% respectively.

Distribution

Telmisartan is highly bound to plasma proteins (>99.5%) mainly albumin and α_1-acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution of telmisartan is approximately 500 litres indicating additional tissue binding.

Metabolism

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide; the glucuronide of the parent compound is the only metabolite in human plasma and urine.

Excretion

Telmisartan is excreted almost entirely in the feces via bile, mainly as an unchanged drug. Total plasma clearance of telmisartan is >800mL/min. The terminal elimination half-life of telmisartan is about 24 hours.

Special population

Elderly

Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%. The pharmacokinetics of telmisartan does not differ between the elderly and those younger than 65 years of age.

Renal Impairment

The pharmacokinetics of amlodipine is not significantly influenced by renal insufficiency. In patients with mild to moderate renal insufficiency, doubling of plasma concentration of telmisartan occur. However, plasma concentration is lowered in patients with renal insufficiency undergoing dialysis.

Hepatic Impairment

Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40% to 60%. The plasma concentration of telmisartan is also increased in such patients with reduction in clearance and absolute bioavailability approaches to 100%.

THERAPEUTIC INDICATIONS

Tasmi-AM (Amlodipine + Telmisartan) is indicated for:

- the treatment of hypertension alone or with other antihypertensive agents.
- the initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

DOSAGE & ADMINISTRATION

Tasmi-AM (Amlodipine + Telmisartan) is effective in the treatment of hypertension in once daily doses of amlodipine as 2.5mg to 10mg and telmisartan as 20mg to 80mg. It may be taken with or without food. Tasmi-AM (Amlodipine + Telmisartan) is formulated for oral administration in the following strength combinations:

- Tasmi-AM Tablets 5mg + 40mg
- Tasmi-AM Tablets 5mg + 80mg
- Tasmi-AM Tablets 10mg + 40mg
- Tasmi-AM Tablets 10mg + 80mg

Dosage must be individualized and may be increased after at least 2 weeks. Most of the antihypertensive effect is apparent within 2 weeks and maximal reduction is generally attained after 4 weeks. The maximum recommended dose of Tasmi-AM (Amlodipine + Telmisartan) is 10mg + 80mg once daily.

Replacement Therapy

Patients receiving amlodipine and telmisartan from separate tablets may instead receive Tasmi-AM (Amlodipine + Telmisartan) Tablets containing the same component doses once daily. When substituting for individual components, increase the dose of Tasmi-AM (Amlodipine + Telmisartan) Tablets if blood pressure control has not been satisfactory.

Add-on Therapy for Patients with Hypertension Not Adequately Controlled on Antihypertensive Monotherapy

Tasmi-AM (Amlodipine + Telmisartan) Tablets may be used to provide additional blood pressure lowering for patients not adequately controlled with amlodipine (or another dihydropyridine calcium channel blocker) alone or with telmisartan

(or another angiotensin receptor blocker) alone.
Patients treated with 10mg amlodipine who experience any dose-limiting adverse reactions such as edema, may be switched to Tasmi-AM (Amlodipine + Telmisartan) Tablets 5mg + 40mg once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

Initial Therapy
A patient may be initiated on Tasmi-AM (Amlodipine + Telmisartan) Tablets if it is unlikely that control of blood pressure would be achieved with a single agent. The usual starting dose of Tasmi-AM (Amlodipine + Telmisartan) Tablets is 5mg + 40mg once daily. Patients requiring larger blood pressure reductions may be started on Tasmi-AM (Amlodipine + Telmisartan) Tablets 5mg + 80mg once daily.
Initial therapy with Tasmi-AM (Amlodipine + Telmisartan) Tablets is not recommended in patients ≥75 years old or with hepatic impairment. Correct imbalances of intravascular volume-or salt-depletion, before initiating therapy with Tasmi-AM (Amlodipine + Telmisartan) Tablets.

Special population
Elderly
In most patients, initiate amlodipine therapy at low doses. Titrate slowly in patients 75 years of age and older.

Renal Impairment
No initial dosage adjustment is required for patients with mild or moderate renal insufficiency. Titrate slowly in patients with severe renal insufficiency.

Hepatic Impairment
Initiate therapy at low doses of amlodipine and telmisartan. Titrate slowly in patients with hepatic insufficiency.

ADVERSE REACTIONS
Common
Dizziness and peripheral edema.

Uncommon
Somnolence, migraine, headache, paraesthesia, vertigo, bradycardia, palpitations, hypotension, orthostatic hypotension, flushing, cough, abdominal pain, diarrhea, nausea, pruritis, arthralgia, muscle spasms (cramps in legs), myalgia, erectile dysfunction, asthenia, chest pain, fatigue, edema and increased hepatic enzymes.

Rare
Cystitis, depression, anxiety, insomnia, syncope, peripheral neuropathy, hypoaesthesia, dysgeusia, tremor, vomiting, gingival hypertrophy, dyspepsia, dry mouth, eczema, erythema, rash, back pain in extremity (leg pain), nocturia, malaise and increase blood uric acid.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
The combination of amlodipine and telmisartan is contraindicated in patients who are hypersensitive to the active substances, to dihydropridine derivatives, or to any of the excipients.

PRECAUTIONS
- In patients with an activated renin-angiotensin system such as volume or salt-depleted patients (e.g; patients receiving high doses of diuretics) symptomatic hypotension may occur after initiation of therapy with combination of amlodipine and telmisartan tablets. Correction of this condition prior to administration of this combination or close medical supervision at the start of treatment with reduced dose is recommended.
- Close monitoring is required when administering amlodipine in patients with severe aortic stenosis as it may cause acute hypotension.
- Particular caution should be exercised when administering the combination of amlodipine and telmisartan to patients with hepatic insufficiency or biliary obstructive disorders.
- Hyperkalemia may occur with angiotensin receptors blockers like telmisartan, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on drugs that increase potassium levels. Periodic determinations of serum electrolytes are recommended to detect possible electrolyte imbalances, particularly in patients at risk.
- Treatment with angiotensin receptor antagonists should be given with caution in patients whose renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system e.g., patients with severe congestive heart failure or renal dysfunction.
- Dual blockade of renin-angiotensin-aldosterone system (e.g; by adding an angiotensin converting enzyme (ACE)-inhibitor to an angiotensin II receptor antagonist) is not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function.
- Periodic monitoring of potassium and creatinine serum levels is recommended in patients with a recent kidney transplant as amlodipine and telmisartan are not dialyzable.
- It is recommended to closely monitor the patients with heart failure while administering amlodipine.
- Caution should be taken with amlodipine, particularly in patients, with severe obstructive coronary artery disease.

Pregnancy
The combination of amlodipine and telmisartan is contraindicated in second and third trimesters of pregnancy. When pregnancy is detected it should be discontinued as soon as possible because it can cause fetal and neonatal morbidity and death.

Nursing Mothers
The combination of amlodipine and telmisartan is not recommended during breast feeding. It is advised to either discontinue the drug or nursing.

DRUG INTERACTIONS
Other antihypertensive medicinal products
Concomitant use of other antihypertensive medicinal products can increase the blood pressure lowering effects of the combination of amlodipine and telmisartan tablets.

Medicinal products with blood pressure lowering potential
Concomitant use of medicinal products e.g; baclofen, amifostine, neuroleptics or antidepressants may potentiate the hypotensive effects of all antihypertensives including the combination of amlodipine and telmisartan tablets.

Corticosteroids
Co-administration of the combination of amlodipine and telmisartan with corticosteroids causes reduction of the antihypertensive effect.

Potassium sparing diuretics or Potassium supplements
Concomitant use of angiotensin II receptor antagonists such as telmisartan with potassium sparing diuretics or potassium supplements may attenuate diuretic induced potassium loss.

Lithium
Concomitant administration of angiotensin II receptor antagonists including telmisartan with lithium causes reversible increases in serum lithium concentrations and toxicity.

Non-steroidal anti-inflammatory medicines
Co-adminstration of NSAID's (i.e. acetyl salicylic acid at anti-inflammatory dosage regimen, COX-2 inhibitors and non-selective NSAID's) may reduce the antihypertensive effect of angiotensin II receptor antagonists.

CYP3A4 Inhibitors
Co-administration of amlodipine with CYP3A4 inhibitors like erythromycin in young patients and diltiazem in elderly patients respectively increases the plasma concentration of amlodipine by 22% and 50% respectively. The strong inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem.

CYP3A4 inducers
Concomitant use of amlodipine with CYP3A4 inducers (i.e; rifampicin, Hypericum perforatum) may lead to reduced plasma concentrations of amlodipine.

OVERDOSAGE
Symptoms
Overdose with amlodipine may result in excessive peripheral vasodilation and possibly reflex tachycardia. Marked and prolonged systemic hypotension up to and including shock with fatal outcome.
The most prominent manifestations of telmisartan overdose is hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine and acute renal failure.

Treatment
The patient should be closely monitored and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of overdose of both amlodipine and telmisartan. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position with elevation of extremities, with salt and volume replacement given quickly. Supportive treatment should be instituted. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Amlodipine and telmisartan are not removed by hemodialysis.

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Tasmi-AM (Amlodipine + Telmisartan) Tablets 5mg + 40mg are available in blister pack of 14's.
Tasmi-AM (Amlodipine + Telmisartan) Tablets 5mg + 80mg are available in blister pack of 14's.
Tasmi-AM (Amlodipine + Telmisartan) Tablets 10mg + 40mg are available in blister pack of 14's.
Tasmi-AM (Amlodipine + Telmisartan) Tablets 10mg + 80mg are available in blister pack of 14's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
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29-30/27, K.I.A., Karachi, Pakistan

L-200013536