Telsarta-A®

5/40
10/40
5/80
10/80

(Amlodipine+Telmisartan USP)

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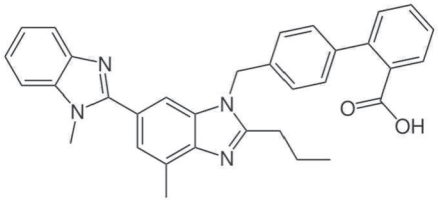
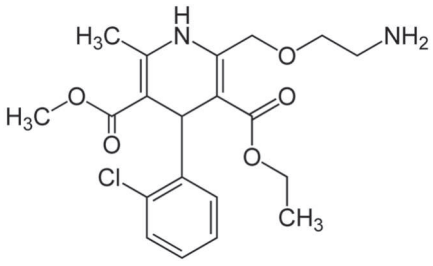
Composition:
Telsarta A 5/40 mg
Each tablet contains Amlodipine… 5mg and Telmisartan…... 40 mg
Telsarta A 10/40 mg
Each tablet contains Amlodipine… 10mg and Telmisartan…. 40 mg
Telsarta A 5/80 mg
Each tablet contains Amlodipine… 5mg and Telmisartan…... 80 mg
Telsarta A 10/80 mg
Each tablet contains Amlodipine… 10mg and Telmisartan…. 80 mg
(USP Specs.)

DESCRIPTION
TELSARTA A is a fixed dose combination of telmisartan and amlodipine. TELSARTA A tablets contain telmisartan, a non-peptide angiotensin II receptor (type AT1) antagonist. 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 (except insoluble in hydrochloric acid), and soluble in strong base. 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 C33H30N4O2 and its structural formula is:



TELSARTA A tablets contain the besylate salt of amlodipine, a dihydropyridine calcium-channel blocker (CCB). Amlodipine besylate is a white to pale yellow crystalline powder, slightly soluble in water and sparingly soluble in ethanol. Amlodipine besylate's chemical name is 3-Ethyl-5-methyl(4RS)-2-[(2-aminoethoxy)methyl]-4-(2 chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate. Its empirical formula is C20H25CIN2O5•C6H6O3S and its structural formula is:



TELSARTA Atablets are formulated in four strengths for oral administration with a combination of amlodipine besylate, equivalent to 5 mg or 10 mg of amlodipine free- base, with 40 mg, or 80 mg of telmisartan provided in the following four combinations: 40/5 mg, 40/10 mg, 80/5 mg, and 80/10 mg.

CLINICAL PHARMACOLOGY
Mechanism of Action
Telmisartan
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 the binding of angiotensin II to the AT1 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 AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT1 receptor than for the AT2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.

Amlodipine
Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions 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. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

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.

Pharmacodynamics
TELSARTA A tablets have been shown to be effective in lowering blood pressure. TELSARTA A is a combination of two drugs with antihypertensive properties: a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker), amlodipine besylate, and an angiotensin II receptor blocker, telmisartan.
Both telmisartan and amlodipine, lower blood pressure by reducing peripheral resistance but through complementary mechanisms.

Telmisartan
In normal volunteers, a dose of telmisartan 80 mg inhibited the pressor response to an intravenous infusion of angiotensin II by about 90% at peak plasma concentrations with approximately 40% inhibition persisting for 24 hours.

Amlodipine
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. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily 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 the height of pretreatment elevation; 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 pressure (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

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

Telmisartan
Following oral administration, peak concentrations (Cmax) of telmisartan are reached in 0.5 to 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 and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20 to 160 mg, with greater than proportional increases of plasma concentrations (Cmax and AUC) with increasing doses. 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% to 25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Amlodipine
Peak plasma concentrations of amlodipine are reached 6 to 12 hours after administration of amlodipine alone. Absolute bioavailability has been

estimated to be between 64% and 90%. The bioavailability of amlodipine is not altered by the presence of food.
Elimination of amlodipine 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.

DISTRIBUTION
Telmisartan
Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and •1 - 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.

Amlodipine
The apparent volume of distribution of amlodipine is 21 L/kg. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

METABOLISM AND ELIMINATION
Telmisartan
Following either intravenous or oral administration of 14C-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).

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. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.
Total plasma clearance of telmisartan is >800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

Amlodipine
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.

SPECIAL POPULATIONS
Renal Insufficiency
Telmisartan: No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration.
Amlodipine: The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Hepatic Insufficiency
Telmisartan: In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100%.
Amlodipine: Patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%. Therefore, start with a low initial dose of amlodipine.

Gender
Plasma concentrations of telmisartan are generally 2 to 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.

Geriatric Patients
Telmisartan: The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years.
Amlodipine: Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%. Therefore, start with a low initial dose of amlodipine.

INDICATIONS AND USAGE
TELSARTA A is an angiotensin II receptor blocker (ARB) and a dihydropyridine calcium channel blocker (DHP-CCB) combination product indicated for the treatment of hypertension alone or with other antihypertensive agents.
TELSARTA A tablets are indicated as initial therapy in patients likely to need multiple antihypertensive agents to achieve their blood pressure goals.

DOSAGE AND ADMINISTRATION
Substitute TELSARTA A for its individually titrated components for patients on amlodipine and telmisartan. TELSARTA A may also be given with increased amounts of amlodipine, telmisartan, or both, as needed.

Use TELSARTA A tablets 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.
Dosage may be increased after at least 2 weeks to a maximum dose of 80/10 mg once daily, usually by increasing one component at a time but both components can be raised to achieve more rapid control. Majority of antihypertensive effect is attained within 2 weeks. Initiate with 40/5 mg or 80/5 mg once daily.
Switch patients who experience dose-limiting adverse reactions on amlodipine to TELSARTA A tablets containing a lower dose of that component.

DOSAGE FORMS AND STRENGTHS
Tablets: 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg

CONTRAINDICATIONS
Known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan, amlodipine or any other component of this product.

WARNINGS AND PRECAUTIONS
Avoid fetal or neonatal exposure.
Hypotension: Correct any volume or salt depletion before initiating therapy. Observe for signs and symptoms of hypotension.
Titrate slowly in patients with hepatic or severe renal impairment.
Heart failure: Monitor for worsening.
Avoid concomitant use of an ACE inhibitor and angiotensin receptor blocker.
Myocardial infarction: Uncommonly, initiating a CCB in patients with severe obstructive coronary artery disease may precipitate myocardial infarction or increased angina.

ADVERSE REACTIONS
In the placebo-controlled factorial design study, the most common reasons for discontinuation of therapy were peripheral edema, dizziness, and hypotension.

DRUG INTERACTIONS
NSAIDS: Increased risk of renal impairment and loss of anti hypertensive effect.
If simvastatin is co-administered with amlodipine, do not exceed doses greater than 20 mg daily of simvastatin.
USE IN SPECIFIC POPULATIONS
Patients •'3d75 years of age or hepatically impaired patients: Start with amlodipine or add amlodipine 2.5 mg to Telmisartan.
Nursing Mothers: Choose to discontinue nursing or drug.

OVERDOSAGE
Telmisartan
Limited data are available with regard to overdosage in humans. The most likely manifestations 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
Single oral doses of amlodipine maleate equivalent to 40 mg/kg and 100 mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine in dogs (11 or more times the maximum recommended human dose on a mg/m2 basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. 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) who 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 was 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.

HOW SUPPLIED:
Telsarta A 5/40 mg available in a pack of 14 Tablets.
Telsarta A 10/40 mg available in a pack of 10 Tablets.
Telsarta A 5/80 mg available in a pack of 14 Tablets.
Telsarta A 10/80 mg available in a pack of 10 Tablets.

INSTRUCTIONS:
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture. Store below 30°C.
For suspected adverse drug reaction, email us at reports@pharmevo.biz

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call PharmAssist helpline 0800-82222
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