TELDAY *Plus*

(Manufacturer's Specs.)

Telmisartan + Amlodipine

40/5mg, 40/10mg & 80/5mg film coated tablets

TELDAY PLUS 40/5 mg tablets: Each film coated tablet contains: Telmisartan...40mg
Amlodipine as Besylate...5mg

TELDAY PLUS 40/10 mg tablets: Each film coated tablet contains: Telmisartan...40mg
Amlodipine as Besylate...10mg

TELDAY PLUS 80/5 mg tablets: Each film coated tablet contains: Telmisartan...80mg
Amlodipine as Besylate...5mg

DESCRIPTION

TELDAY PLUS is a fixed dose combination of telmisartan and amlodipine. Telmisartan is an angiotensin II receptor blocker (ARB) antagonist and amlodipine is a dihydropyridine calcium channel blocker.

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. Telmisartan has much greater affinity (>3,000 fold) for the AT1 receptor than for the AT2 receptor. Blockade the renin-angiotensin system with ACE inhibitors, which inhibit the bio genesis of angiotensin II from angiotensin 1, 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. 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. 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

Telmisartan:

Telmisartan is rapidly absorbed from the gastrointestinal tract. The absolute bioavailability is dose dependent and is about 42% after a 40 mg dose and 58% after a 160 mg dose. Peak plasma concentration of telmisartan reached about 0.5 to 1 hour after an oral dose. Telmisartan is over 99% bound to plasma proteins. It is excreted almost entirely in the via bile, mainly as unchanged drug. The terminal elimination half-life is about 24 hours.

Amlodipine:

Amlodipine is well absorbed after oral doses and peak blood concentration occurs after 6 to 12 hours. The bioavailability varies but is usually about 60 to 65%. Amlodipine is reported to be about 98% bound to plasma proteins. It has a prolonged terminal elimination half-life of 35 to 50 hours and steady-state plasma concentrations are not achieved until after 7 to 8 days of use. Amlodipine is extensively metabolized in the liver; metabolites are mostly excreted in urine, with less than 10% of a dose as unchanged drug. Amlodipine is not removed by dialysis.

INDICATIONS AND USAGE

TELDAY PLUS tablets are indicated as initial therapy in patients likely to need multiple antihypertensive agents to achieve their blood pressure goals and for the treatment of hypertension alone or with other antihypertensive agents to lower blood pressure.

DOSAGE AND ADMINISTRATION

Telmisartan is an effective treatment of hypertension in once daily doses of 20 to 80 mg while amlodipine is effective in doses of 2.5 to 10 mg. 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 **TELDAY PLUS** tablets is 80/10 mg once daily. It may be taken with or without food. Patients receiving amlodipine and telmisartan from separate tablets may instead receive **TELDAY PLUS** tablets containing the same component doses once daily. **TELDAY PLUS** 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. The usual starting dose of **TELDAY PLUS** is 40/5 mg once daily. Patients requiring larger blood pressure reductions may be started on Misar AM 80/5 mg once daily. Patients treated with 10 mg amlodipine who experience any dose-limiting adverse reactions such as edema, may be switched to **TELDAY PLUS** 40/5 mg tablets once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response. Initial therapy with **TELDAY PLUS** is not recommended in patients > 75 years old or with hepatic impairment.

ADVERSE REACTIONS

The reported adverse events are peripheral edema, dizziness, back pain, edema (other than peripheral edema), hypotension, and syncope. Peripheral edema is a known, dose-dependent adverse reaction of amlodipine, but not of telmisartan.

Telmisartan:

The reported adverse events of the telmisartan are upper respiratory tract infection, back pain, sinusitis, diarrhea, pharyngitis, influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, hypertension, chest pain, nausea, cough and peripheral edema. These are also reported events includes headache, dizziness, asthenia, 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, urinary tract infection, erectile dysfunction, muscle cramps (including leg cramps), bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, and increased CPK, anaphylactic reaction, tendon pain (including tendonitis, tenosynovitis), drug eruption (e.g., toxic skin eruption mostly reported as toxicoderma, rash, and urticaria), hypoglycemia (in diabetic patients), and angioedema (with fatal outcome). In rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including telmisartan and occasional elevations of liver chemistries occurred in patients treated with telmisartan.

Amlodipine:

The most common side effects were headache, dizziness, flushing, palpitations, edema, fatigue, nausea, abdominal pain and somnolence. The also reported events of amlodipine are cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia. The events where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship. Arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis, hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo, anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia, change of bowel habit, allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease, arthralgia, arthrosis, muscle cramps, myalgia, sexual dysfunction, insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization, mood change, dyspnea, epistaxis, angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular, abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus, micturition frequency, micturition disorder, nocturia, dry mouth, sweating increased, hyperglycemia, thirst, leukopenia, purpura, thrombocytopenia gynecomastia, hepatic enzyme elevation and extrapyramidal disorder.

DRUG INTERACTIONS

The pharmacokinetics of amlodipine and telmisartan are not altered when the drugs are co-administered.

Drug Interactions with Telmisartan

Aliskiren: Do not co-administer aliskiren with **TELDAY PLUS** in patients with diabetes. Avoid use of aliskiren with **TELDAY PLUS** in patients with renal impairment (GFR <60 mL/min).

Digoxin:

Monitor digoxin levels when initiating, adjusting, and discontinuing telmisartan for the purpose of keeping the digoxin level within the therapeutic range.

Lithium:

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including telmisartan. Therefore, monitor serum lithium levels during concomitant use.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (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 angiotensin II receptor antagonists, 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. attenuated by NSAIDs including selective COX-2 inhibitors.

Ramipril and Ramiprilat:

Co-administration of telmisartan and ramipril is not recommended. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan.

Other Drugs:

Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin, or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects in vitro on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

Drug Interactions with Amlodipine Amlodipine has been safely administered with thiazide diuretics, beta- blockers, enzyme inhibitors, long-acting nitrates, angiotensin-converting sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti- inflammatory drugs, antibiotics, and oral hypoglycemic drugs. Simvastatin: Limit the dose of simvastatin in patients on amlodipine to 20 mg daily. Immunosuppressants: Amlodipine may increase the systemic sure, of cyclosporine or tacrolimus when co-administered. Frequent exposure monitoring of trough blood levels of cyclosporine and tacrolimus s recommended and adjust the dose when appropriate. The following have no clinically relevant effects on the pharmacokinetics of amlodipine: cimetidine, grapefruit juice, magnesium and aluminum hydroxide antacid, sildenafil.

Hydroxide

Amlodipine has no clinically relevant effects on the pharmacokinetics or pharmacodynamics of the following: atorvastatin, digoxin, warfarin. CYP3A4 inhibitors: Strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors. CYP3A4 Inducers: Patients should be monitored for adequate clinical effect when amlodipine is co-administered with CYP3A4 inducers.

CONTRAINDICATIONS

TELDAY PLUS tablets are contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan, amlodipine, or any other component of this product.

- Do not co-administer aliskiren with **TELDAY PLUS** in patients with diabetes.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D Use of drugs that act on the renin-angiotensin system 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. When pregnancy is detected, discontinue **TELDAY PLUS** as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Misar AM, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to **TELDAY PLUS** for hypotension, oliguria, and hyperkalemia.

Nursing Mothers

Because of the potential for adverse effects on the nursing infant, decide whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. It is not known whether telmisartan is excreted in human milk. It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended to discontinue nursing while amlodipine is administered.

Pediatric Use

Safety and effectiveness of telmisartan / amlodipine in pediatric patients have not been established. If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Geriatric Use

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40% to 60%, and a lower initial dose may be required.

Hepatic Insufficiency

Monitor carefully and up-titrate slowly in patients with biliary obstructive disorders or hepatic insufficiency Since patients with hepatic impairment have decreased clearance of amlodipine.

WARNINGS AND PRECAUTIONS

Fetal Toxicity

Avoid fetal or neonatal exposure.

Hypotension

In patients with an activated renin-angiotensin system, 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 **TELDAY PLUS** tablets. Either correct this condition prior to administration of **TELDAY PLUS** tablets, or start treatment under close medical supervision with a reduced dose.

Hyperkalemia

Hyperkalemia may occur in patients on 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. Impaired Hepatic and Renal Function Caution should be exercised in hepatic and renal impairment patients. Titrate slowly in hepatic and renal impairment patients. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Inhibiting the renin-angiotensin-aldosterone system, anticipate changes in renal function in susceptible individuals. Dual Blockade of the Renin-Angiotensin-Aldosterone System Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on TELDAY PLUS and other agents that affect the RAS.

Diabetics:

Do not co-administer aliskiren with **TELDAY PLUS** in patients with diabetes.

Risk of Myocardial infarction or Increased Angina

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.

Heart Failure

Closely monitor patients with heart failure.

OVERDOSAGE

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. The amlodipine overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. 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.

DOSAGE & INSTRUCTIONS:

Use as directed by the physician. For details, see enclosed leaflet.To be sold on the prescription of a registered medical practitioner only. Keep all medicines out of the reach of children. Store at 20°C-25°C. Protect from light and moisture.
(excursions permitted to 15°C-30°C).

PACK SIZE

TELDAY PLUS 40/5mg tablets: Blister Pack of 14's.
TELDAY PLUS 40/10mg tablets: Blister Pack of 14's.
TELDAY PLUS 80/5mg tablets: Blister Pack of 14's.

TO BE SOLD ON THE PRESCRIPTION OF A REGISTERED MEDICAL PRACTITIONER ONLY.
KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

Lactose & Gluten Free

ٹیل ڈے پلس

ٹیلمیسارٹن + املوڈپائن

40/5 ملی گرام، 40/10 ملی گرام اور 80/5 ملی گرام فلم کوٹڈ گولیاں

خوراک و ہدایات:

ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت کی جائے۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

دوا کو 20°C-25°C درجہ حرارت پر نمی اور روشنی سے محفوظ رکھیں۔

(درجہ حرارت کی حد 15°C سے 30°C ہے۔)

NEXT PHARMACEUTICAL
Manufactured by:
NEXT Pharmaceutical Products (Pvt.) Ltd.
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