120x260mm

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Misar AM®

(Telmisartan + Amlodipine)

Highnoon

COMPOSITION
Misar AM 40mg/5mg Tablet: Each tablet contains:
Telmisartan 40mg
Amlodipine (as Besylate) 5mg
Misar AM 40mg/10mg Tablet: Each tablet contains:
Telmisartan 40mg
Amlodipine (as Besylate) 10mg
Misar AM 80mg/5mg Tablet: Each tablet contains:
Telmisartan 80mg
Amlodipine (as Besylate) 5mg
Misar AM 80mg/10mg Tablet: Each tablet contains:
Telmisartan 80mg
Amlodipine (as Besylate) 10mg

DESCRIPTION
MISAR AM 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 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.
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 faeces 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 occur after 6 to 12 hour. 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
It is 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 is 80/10mg once daily. It may be taken with or without food.
Patients receiving amlodipine and telmisartan from separate tablets may instead receive Misar AM tablets containing the same component doses once daily. It 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 (Telmisartan / Amlodipine combination) is 40/5mg once daily. Patients requiring larger blood pressure reductions may be started on Misar AM 80/5mg once daily.
Patients treated with 10 mg amlodipine who experience any dose-limiting adverse reactions such as edema, may be switched to (Telmisartan / Amlodipine combination)
Misar AM 40/5mg tablets once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.
Initial therapy with (Telmisartan / Amlodipine combination) 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.

Telmisartan: The reported adverse events of the telmisartan are upper respiratory tract infection, back pain, sinusitis, diarrhoea, pharyngitis, influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, hypertension, chest pain, nausea, cough, peripheral edema, asthenia, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, impotence, sweating increased, flushing, fever, malaise, leg pain, palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG, insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia, flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, nonspecific gastrointestinal disorders, muscle cramps (including leg cramps), arthritis, arthralgia, gout, hypercholesterolemia, diabetes mellitus, infection, fungal infection, abscess, otitis media, asthma, bronchitis, rhinitis, dyspnea, epistaxis, dermatitis, rash, eczema, pruritus, micturition frequency, cystitis, cerebrovascular disorder, abnormal vision, conjunctivitis, tinnitus, earache, decrease hemoglobin, allergy, liver enzyme elevation and increase creatinine.
The additional reported adverse events are: weakness, erythema, atrial fibrillation, congestive heart failure, myocardial infarction, increased blood pressure, hypotension (including postural hypotension), hyperkalemia, syncope, erectile dysfunction, 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), weakness, hyponatremia, angioedema (with fatal outcome), depression and rhabdomyolysis.

Amlodipine: The most common side effects were headache, dizziness, flushing, palpitations, edema, fatigue, nausea, abdominal pain, somnolence, 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, increased sweating, hyperglycemia, thirst, leukopenia, purpura, thrombocytopenia, 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, gynecomastia, jaundice, hepatic enzyme elevation, drowsiness, gastrointestinal discomfort, joint disorder, muscle complaint, vision disorder, xerophthalmia, hyperhidrosis, sensation abnormal, urinary disorder, confusion, leucopenia, muscle tone increased, photosensitivity reaction, Stevens Johnson Syndrome, pulmonary oedema, extrapyramidal symptoms, paresthesia, pancreatitis.

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

Drug Interactions with Telmisartan
- Do not co-administer aliskiren with (telmisartan and amlodipine combination) in patients with diabetes. Avoid use of aliskiren with (telmisartan and amlodipine combination) in patients with renal impairment (GFR <60 mL/min).
- Monitor digoxin levels when initiating, adjusting, and discontinuing telmisartan for the purpose of keeping the digoxin level within the therapeutic range.
- Reversible increase 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.
- 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. The antihypertensive effect of angiotensin II receptor antagonists, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

Drug Interactions with Amlodipine
- Amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.
- Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.
- Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and adjust the dose when appropriate.
- Cimetidine, grapefruit juice, magnesium and aluminum hydroxide antacid, sildenafil, atorvastatin, digoxin and warfarin have no clinically relevant effects on the pharmacokinetics of amlodipine.
- 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.
- Patients should be monitored for adequate clinical effect when amlodipine is co-administered with CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone, rifampicin, St. John's Wort).

CONTRAINDICATIONS
- It is contraindicated in patient with known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan, amlodipine, or any other component of this product.
- Do not co-administer aliskiren with (telmisartan and amlodipine combination) in patients with diabetes.

USE IN SPECIFIC POPULATIONS
Pregnancy
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 (telmisartan and amlodipine combination) 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 (telmisartan and amlodipine combination), 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 (telmisartan and amlodipine combination) for hypotension, oliguria, and hyperkalemia.

Nursing Mothers
Because of the potential for serious adverse reactions in the breastfed infant including hypotension, hyperkalemia and renal impairment, advise a nursing woman not to breastfeed during treatment with (telmisartan and amlodipine combination). 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. In the absence of this information, it is recommended to discontinue nursing while amlodipine is administered.

Paediatric Use
Safety and effectiveness of telmisartan / amlodipine in paediatric patients have not been established. If oliguria or hypotension occurs, direct attention towards 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
No overall differences in efficacy or safety of (telmisartan and amlodipine combination) were observed in this patient population.

Telmisartan: No overall differences in effectiveness and safety were observed in these patients compared to younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Amlodipine: 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. Since patients age 75 and older have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5 mg to telmisartan. The lowest dose of (telmisartan and amlodipine combination) is 40/5 mg; therefore, initial therapy with (telmisartan and amlodipine combination) is not recommended in patients 75 years of age and older.

Hepatic Insufficiency
Monitor carefully and up-titrate slowly in patients with biliary obstructive disorders or hepatic insufficiency and older. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5mg to telmisartan. The lowest dose of (telmisartan and amlodipine combination) is 40/5mg; therefore, initial therapy with (telmisartan and amlodipine combination) is not recommended in hepatically impaired patients.

WARNINGS AND PRECAUTIONS
Fetal Toxicity
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 it as soon as possible.

Hypotension
Telmisartan: 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 (telmisartan and amlodipine combination). Either correct this condition prior to administration of (telmisartan and amlodipine combination), or start treatment under close medical supervision with a reduced dose. If hypotension does occur, place the patient in the supine position and, if necessary, give an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

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

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 Function
Telmisartan: The majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Initiate telmisartan at low doses and titrate slowly in these patients.
Amlodipine: Amlodipine is extensively metabolized by the liver and the plasma elimination half-life is 56 hours in patients with impaired hepatic function. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine at 2.5 mg in patients with hepatic impairment. The lowest dose of (telmisartan and amlodipine combination) is 40/5 mg; therefore, initial therapy with this medicine is not recommended in hepatically impaired patients.

Impaired Renal Function
Telmisartan
In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists have 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.

Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAS)
Telmisartan
Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on (telmisartan and amlodipine combination) and other agents that affect the RAS.
Do not co-administer aliskiren with (telmisartan and amlodipine combination) in patients with diabetes. Avoid concomitant use of aliskiren with (telmisartan and amlodipine combination) in patients with renal impairment (GFR <60 mL/min /1.73 m^2).

Risk of Myocardial Infarction or Increased Angina
Amlodipine
Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of (telmisartan and amlodipine combination), particularly in patients with severe obstructive coronary artery disease.

Heart Failure
Amlodipine
Closely monitor patients with heart failure.

OVERDOSAGE
Telmisartan: 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: 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 AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION
Misar AM 40mg/5mg Tablets: Alu. Alu. Blister Pack of 2 x 7's. Alu. Alu. Blister Pack of 2 x 10's.
Misar AM 40mg/10mg Tablets: Alu. Alu. Blister Pack of 2 x 7's. Alu. Alu. Blister Pack of 2 x 10's.
Misar AM 80mg/5mg Tablets: Alu. Alu. Blister Pack of 2 x 7's. Alu. Alu. Blister Pack of 2 x 10's.
Misar AM 80mg/10mg Tablets: Alu. Alu. Blister Pack of 1 x 10's. Alu. Alu. Blister Pack of 2 x 10's.

مِسار اے ایم®

(ٹیلمی سارٹن + ایملوڈِپین)

خوراک و ہدایات:

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

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