Mesartanveros Tablets

Amlodipine 10 mg
Telmisartan 80 mg

FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- When pregnancy is detected, discontinue MESARTANVEROSE as soon as possible [see Warnings and Precautions].
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus [see Warnings and Precautions].

1 INDICATIONS AND USAGE

MESARTANVEROSE (telmisartan/amlodipine) tablets are indicated for the treatment of hypertension, alone or with other antihypertensive agents to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including angiotensin II receptor blockers and dihydropyridine calcium channel blockers. There are no controlled trials demonstrating risk reduction with telmisartan & amlodipine tablets .

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals.

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal. Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

MESARTANVEROSE tablets may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

Base the choice of MESARTANVEROSE tablets as initial therapy for hypertension on an assessment of potential benefits and risks including whether the patient is likely to tolerate the starting dose of MESARTANVEROSE tablets.

Patients with moderate or severe hypertension are at relatively high risk for cardiovascular events (such as strokes, heart attacks, and heart failure), kidney failure, and vision problems, so prompt treatment is clinically relevant. Consider the patient's baseline blood pressure, the target goal, and the incremental likelihood of achieving goal with a combination compared with monotherapy when deciding whether to use MESARTANVEROSE tablets as initial therapy. Individual blood pressure goals may vary based upon the patient's risk.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

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 telmisartan & amlodipine tablets is 80/10 mg once daily.
The adverse reactions of telmisartan are uncommon and independent of dose; those of amlodipine are a mixture of dose-dependent phenomena (primarily peripheral edema) and dose-independent phenomena, the former much more common than the latter [see Adverse Reactions].
MESARTANVEROSE may be taken with or without food.

2.2 Replacement Therapy

Patients receiving amlodipine and telmisartan from separate tablets may instead receive telmisartan & amlodipine tablets containing the same component doses once daily. When substituting for individual components, increase the dose of telmisartan & amlodipine tablets if blood pressure control has not been satisfactory.

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

Telmisartan & amlodipine 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 10 mg amlodipine who experience any dose-limiting adverse reactions such as edema, may be switched to telmisartan & amlodipine 40/5 mg tablets once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response [see Adverse Reactions].

2.4 Initial Therapy

A patient may be initiated on telmisartan & amlodipine tablets if it is unlikely that control of blood pressure would be achieved with a single agent. The usual starting dose of telmisartan & amlodipine tablets is 40/5 mg once daily. Patients requiring larger blood pressure reductions may be started on telmisartan & amlodipine 80/5 mg tablets once daily.

Initial therapy with telmisartan & amlodipine tablets is not recommended in patients ≥75 years old or with hepatic impairment [see Dosage and Administration , Warnings and Precautions , and Use in Specific Populations].
Correct imbalances of intravascular volume- or salt-depletion, before initiating therapy with telmisartan & amlodipine tablets [see Warnings and Precautions].

2.5 Dosing in Specific Populations

Renal Impairment
No initial dosage adjustment is required for patients with mild or moderate renal impairment. Titrate slowly in patients with severe renal impairment.
Hepatic Impairment
In most patients, initiate amlodipine therapy at 2.5 mg. Titrate slowly in patients with hepatic impairment.
Patients 75 Years of Age and Older
In most patients, initiate amlodipine therapy at 2.5 mg. Titrate slowly in patients 75 years of age and older.

3 DOSAGE FORMS AND STRENGTH

MESARTANVEROSE tablets : 10 mg amlodipine (as amlodipine besylate)/80 mg telmisarten .

4 CONTRAINDICATIONS

The concomitant use of amlidupine/telmisartan aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) .

MESARTANVEROSE tablets are contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan, amlodipine, or any other component of this product [see Adverse Reactions].
Do not co-administer aliskiren with MESARTANVEROSE in patients with diabetes [see Drug Interactions].

5 WARNINGS AND PRECAUTIONS

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACEinhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended .

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

5.1 Fetal Toxicity

Pregnancy Category D

Telmisartan

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 MESARTANVEROSE as soon as possible [see Use in Specific Populations].

5.2 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 MESARTANVEROSE tablets. Either correct this condition prior to administration of MESARTANVEROSE tablets, 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.

5.3 Hyperkalemia

Telmisartan

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.

5.4 Patients with Impaired Hepatic Function

Telmisartan

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. Initiate telmisartan at low doses and titrate slowly in these patients [see Dosage and Administration , Use in Specific Populations, and Clinical Pharmacology].

Amlodipine

Amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t1/2) 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 & amlodipine is 40/5 mg tablets ; therefore, initial therapy with telmisartan & amlodipine tablets is not recommended in hepatically impaired patients [see Use in Specific Populations].

5.5 Renal Function Impairment

Telmisartan

As a consequence of inhibiting the renin-angiotensin-aldosterone system, anticipate changes in renal function 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 or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) 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 [see Clinical Pharmacology] .

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 in patients with unilateral or bilateral renal artery stenosis, but anticipate an effect similar to that seen with ACE inhibitors.

5.6 Dual Blockade of the Renin-Angiotensin-Aldosterone System

Telmisartan

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported. Dual blockade of the renin-angiotensin-aldosterone system (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should include close monitoring of renal function.

Pateients with atherosclerotic disease or diabetes with end-organ damage and receiving the combination of telmisartan & ramipril experienced an increased incidence of renal dysfunction (e.g., acute renal failure) compared with pateients receiving telmisartan alone or ramipril alone. Concomitant use of telmisartan and ramipril is not recommended.

5.7 Risk of Myocardial Infarction or Increased Angina

Amlodipine

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of telmisartan & amlodipine tablets , particularly in patients with severe obstructive coronary artery disease.

5.8Heart Failure

Amlodipine

Closely monitor patients with heart failure.

Amlodipine (5 to 10 mg per day) has been studied in patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine in patients with NYHA class II/III heart failure, showed no evidence of worsening of heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF. In patients with NYHA class III or IV heart failure without evidence of underlying ischemic disease, on stable doses of ACE inhibitor, digitalis, and diuretics and receive amlodipine, There were reports of pulmonary edema in the patients on amlodipine & no statistically difference in the primary end point of all cause mortality .

6 ADVERSE REACTIONS

Telmisartan&amlodipine Tablets

Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

The frequency of adverse reactions was not related to gender, age, or race.

The adverse reactions that occurred in patients treated with telmisartan & amlodipine tablets were peripheral edema, dizziness, and back pain. Edema (other than peripheral edema), hypotension, and syncope were reported in patients treated with telmisaratan & amlodipine tablets.

Discontinuation due to adverse events in the amlodipine/telmisartan treated patients were due to peripheral edema, dizziness, and hypotension .

Peripheral edema is a known, dose-dependent adverse reaction of amlodipine, but not of telmisartan., the incidence of peripheral edema was highest with amlodipine 10 mg monotherapy. The incidence was notably lower when telmisartan was used in combination with amlodipine 10 mg.

Telmisartan

Telmisartan has been evaluated for safety. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

Table 1: Adverse Events Occurring Patients Treated with Telmisartan

Upper respiratory tract infection
Back pain
Sinusitis
Diarrhea
Pharyngitis

In addition to the adverse events in the table, the following events occurred :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 were not dose related & did not correlate with gender , age or race of patients .

In addition to those listed above, adverse events that occurred in patients treated with telmisartan monotherapy 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, hypoesthesia; 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.

A single case of angioedema was reported

Clinical laboratory findings:

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 telmisartan patients. No patients discontinued therapy due to anemia.

Creatinine: A 0.5 mg/dL rise or greater in creatinine was observed in telmisartan 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;. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

Amlodipine

Amlodipine has been evaluated for safety. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity.

Table 2 : Dose-Related Adverse Effects with Amlodipine at Doses of 2.5 mg, 5.0 mg, and 10.0 mg
Adverse Event
Edema
Dizziness
Flushing
Palpitations

Table 3: Adverse Effects Not Clearly Dose Related but Reported
Adverse Event
Headache
Fatigue
Nausea
Abdominal pain
Somnolence

The following events occurred in patients 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 .
Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.
Gastrointestinal: anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia, change of bowel habit; General: allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.
Musculoskeletal System: arthralgia, arthrosis, muscle cramps, myalgia.
Psychiatric: sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization, mood change .
Respiratory System: dyspnea, epistaxis .
Skin and Appendages: angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular .
Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.
Urinary System: micturition frequency, micturition disorder, nocturia.
Autonomic Nervous System: dry mouth, sweating increased.
Metabolic and Nutritional: hyperglycemia, thirst .
Hemopoietic: leukopenia,purpura,thrombocytopenia.
The following events occurred in patients: 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.
Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.
Amlodipine has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.
Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, coronary artery disease, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.
Other adverse reactions :
The following adverse reactions have been identified during post-approval use of telmisartan or amlodipine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to telmisartan or amlodipine. Telmisartan 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, 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). Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including telmisartan. Amlodipine Gynecomastia has been reported infrequently and a causal relationship is uncertain. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.

7 DRUG INTERACTIONS

7.1 Drug Interactions with MESARTANVEROSE Tablets

The pharmacokinetics of amlodipine and telmisartan are not altered when the drugs are co-administered. No drug interaction studies have been conducted with telmisartan & amlodipine tablets and other drugs, although studies have been conducted with the individual amlodipine and telmisartan components of MESARTANVEROSE tablets, as described below:

7.2 Drug Interactions with Telmisartan

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

Digoxin: When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. Therefore, 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.

The antihypertensive effect of angiotensin II receptor antagonists, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

Ramipril and Ramiprilat: Co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state Cmax and AUC of ramipril 2.3- and 2.1-fold, respectively, and Cmax and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, Cmax and AUC of telmisartan decrease by 31% and 16%, respectively. 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. Co-administration of telmisartan and ramipril is not recommended.

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.

7.3 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.

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

The following have no clinically relevant effects on the pharmacokinetics of amlodipine: cimetidine, grapefruit juice, magnesium and aluminum hydroxide antacid, sildenafil.

Amlodipine has no clinically relevant effects on the pharmacokinetics or pharmacodynamics of the following: atorvastatin, digoxin, warfarin.

CYP3A4Inhibitors
Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, 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.

CYP3A4Inducers
No information is available on the quantitative effects of CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone, rifampicin, St. John's Wort) on amlodipine. Patients should be monitored for adequate clinical effect when amlodipine is co-administered with CYP3A4 inducers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D. [See Warnings and Precautions].
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 MESARTANVEROSE as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

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 MESARTANVEROSE, 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 MESARTANVEROSE for hypotension, oliguria, and hyperkalemia [see Use in Specific Populations].

8.2 Nursing Mothers

Telmisartan

It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. 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.

Amlodipine

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.

8.3 Pediatric Use

Neonates with a history of in utero exposure to MESARTANVEROSE:
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.

Safety and effectiveness of MESARTANVEROSE in pediatric patients have not been established.

8.4 Geriatric Use

Telmisartan&amlodipinetablets

No overall differences in efficacy or safety of telmisartan & amlodipine tablets were observed in this patient population.

Telmisartan

No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Amlodipine

No identified differences in responses between the elderly and younger patients. 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 & amlodipine tablet is 40/5 mg; therefore, initial therapy with telmisartan & amlodipine tablets tablets is not recommended in patients 75 years of age and older [see Dosage and Administration].

8.5 Hepatic Insufficiency

Monitor carefully and uptitrate slowly in patients with biliary obstructive disorders or hepatic insufficiency [see Dosage and Administration and Warnings and Precautions]. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5 mg to telmisartan.

The lowest dose of telmisartan and amlodipine tablet is 40/5 mg; therefore, initial therapy with telmisartan and amlodipine tablet is not recommended in hepatically impaired patients [see DOSAGE AND ADMINISTRATION .

8.6 Race

The magnitude of blood pressure lowering in black patients approached that observed in non-black patients .

9 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

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited. 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.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

Telmisartan & amlodipine Tablets
Telmisartan & amlodipine tablets have been shown to be effective in lowering blood pressure.
Telmisartan & amlodipine 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.
Plasma concentration of angiotensin II and plasma renin activity (PRA) increased in a dose-dependent manner after single administration of telmisartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg telmisartan to healthy subjects did not influence plasma aldosterone concentrations. In multiple dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium), or in metabolic function (including serum levels of cholesterol, triglycerides, HDL, LDL, glucose, or uric acid).
In 30 hypertensive patients with normal renal function treated for 8 weeks with telmisartan 80 mg or telmisartan 80 mg in combination with hydrochlorothiazide 12.5 mg, there were no clinically significant changes from baseline in renal blood flow, glomerular filtration rate, filtration fraction, renovascular resistance, or creatinine clearance.
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.
Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers.

11 Pharmacokinetics

Telmisartan & amlodipine Tablets
The pharmacokinetics of amlodipine and telmisartan when combined are similar to the pharmacokinetics of amlodipine and telmisartan when administered separately.
After administering Telmisartan & amlodipine 80/10 mg tablet with a high-fat meal, the total area under the plasma concentration-time curve (AUC) and Cmax for telmisartan decreased by about 24% and 60%, respectively. For amlodipine, AUC and Cmax were not altered [see Dosage and Administration)].
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 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.
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.
MetabolismandElimination
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.

SpecialPopulations

RenalInsufficiency

Telmisartan: No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration [see Warnings and Precautions].

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% [see Warnings and Precautions and Use in Specific Populations].

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.

GeriatricPatients

Telmisartan: The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years [see Dosage and Administration].

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 [see Dosage and Administration].

List of excipients :

Mannitol – meglumine – sodium hydroxide – magnesium stearate –pregelatinized starch – microcrystalline cellulose(Avicel 112) - Sodium starch glycolate (Type A) - Colloidal silicon dioxide(Aerosil 200) – ferric oxide red.

Storage conditions :

Store at temperature not exceeding 30 ° C , in dry place .

Package :

Carton box contains 1 Hard Al/ white opaque PVDC strip of 10 tablets + inner leaflet .

Produced by Averroes pharma for pharmaceutical industries
Block NO.6048,6th industrial zone , sadat city , Egypt .