AMOSTATIN Tablet

(Amlodipine Besylate + Atorvastatin Calcium)

ایموسٹیٹن ٹیبلیٹ

COMPOSITION

Each film coated tablet contains:
Amlodipine Besylate equivalent to 5mg of Amlodipine
Atorvastatin Calcium Trihydrate equivalent to 10mg of Atorvastatin

Amlodipine Besylate equivalent to 5mg of Amlodipine
Atorvastatin Calcium Trihydrate equivalent to 20mg of Atorvastatin

DESCRIPTION

AMOSTATIN (Amlodipine Besylate and Atorvastatin Calcium) tablets combine the long-acting calcium channel blocker amlodipine besylate with the synthetic lipid-lowering agent atorvastatin calcium.

CLINICAL PHARMACOLOGY

Mechanism of Action
AMOSTATIN is a combination of two drugs, a calcium antagonist amlodipine (antihypertensive / antianginal agent) and an HMG-CoA reductase inhibitor atorvastatin. The amlodipine component of AMOSTATIN inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The atorvastatin component of AMOSTATIN is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.

The Amlodipine Component of AMOSTATIN
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. The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium, epinephrine, serotonin, and thromboxane A2 analog in experimental animal models and in human coronary vessels in vitro. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.

The Atorvastatin Component of AMOSTATIN
Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total- C), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of high-density lipoprotein cholesterol HDL-C are associated with a decreased cardiovascular risk. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C. Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles. Atorvastatin reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous familial hypercholesterolemia (FH), nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin also reduces very low-density lipoprotein cholesterol (VLDL-C) and triglycerides (TG) and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

PHARMACOKINETICS AND METABOLISM

Studies with AMOSTATIN: Following oral administration of AMOSTATIN peak plasma concentrations of amlodipine and atorvastatin are seen at 6 to 12 hours and 1 to 2 hours post dosing, respectively. The rate and extent of absorption (bioavailability) of amlodipine and atorvastatin from AMOSTATIN are not significantly different from the bioavailability of amlodipine and atorvastatin administered separately (see above).

The bioavailability of amlodipine from AMOSTATIN was not affected by food. Although food decreases the rate and extent of absorption of atorvastatin from AMOSTATIN by approximately 32% and 11%, respectively, as it does with atorvastatin when given alone. LDL-C reduction is similar whether atorvastatin is given with or without food.

Special Populations
Geriatric
Studies with amlodipine: Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose of amlodipine may be required.
Pediatric
Studies with atorvastatin: Pharmacokinetic data in the pediatric population are not available.
Renal Insufficiency
The pharmacokinetics of amlodipine and atorvastatin are not significantly influenced by renal impairment. Dose adjustment in patients with renal dysfunction is not necessary.
Hemodialysis
While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin and/or amlodipine since both drugs are extensively bound to plasma proteins.

INDICATIONS AND USAGE

AMOSTATIN is indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate.

Amlodipine
1. Hypertension: Amlodipine is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.
2. Coronary Artery Disease (CAD)
Chronic Stable Angina: Amlodipine is indicated for the treatment of chronic stable angina. Amlodipine may be used alone or in combination with other antianginal or antihypertensive agents;

Vasospastic Angina (Prinzmetal's or Variant Angina):Amlodipine is indicated for the treatment of confirmed or suspected vasospastic angina. Amlodipine may be used as monotherapy or in combination with other antianginal drugs.

Atorvastatin
1. Prevention of Cardiovascular Disease: In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, atorvastatin is indicated to:
- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
- Reduce the risk for revascularization procedures and angina
In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, Atorvastatin has been demonstrated to:
- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
2. Heterozygous Familial and Nonfamilial Hypercholesterolemia: Atorvastatin is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia.
3. Elevated Serum TG Levels.
4. Homozygous Familial Hypercholesterolemia: Atorvastatin is indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable;
5. Pediatric Patients: Atorvastatin is indicated as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in children 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the LDL-C levels remain high.

Therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used, in addition to a diet restricted in saturated fat and cholesterol, only when the response to diet and other nonpharmacological measures has been inadequate.

CONTRAINDICATIONS

AMOSTATIN contains atorvastatin and is therefore contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases. AMOSTATIN is contraindicated in patients with known hypersensitivity to any component of this medication.

Pregnancy and Lactation
AMOSTATIN should be administered to women of child bearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

Liver Dysfunction
It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically thereafter. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of AMOSTATIN is recommended.

AMOSTATIN should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of AMOSTATIN .

Skeletal Muscle
Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with the atorvastatin component of AMOSTATIN and with other drugs in the HMG-CoA reductase inhibitor class.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. AMOSTATIN therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Physicians considering combined therapy with AMOSTATIN and fibric acid derivatives, erythromycin, clarithromycin, a combination of ritonavir plus saquinavir or lopinavir plus ritonavir, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug.

In patients taking AMOSTATIN, therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

Since the vasodilation induced by the amlodipine component of AMOSTATIN is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. Nonetheless, caution should be exercised when administering AMOSTATIN as with any other peripheral vasodilator particularly in patients with severe aortic stenosis.

Before instituting therapy with AMOSTATIN, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems.

Use in Patients with Congestive Heart Failure
In general, calcium channel blockers should be used with caution in patients with heart failure.

Beta-Blocker Withdrawal
The amlodipine component of AMOSTATIN is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Endocrine Function
HMG-CoA reductase inhibitors, such as the atorvastatin component of AMOSTATIN interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

DRUG INTERACTIONS

No drug interaction studies have been conducted with AMOSTATIN and other drugs, although studies have been conducted in the individual amlodipine and atorvastatin components, as described below:

Studies with Amlodipine:
In clinical trials, 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.

Studies with Atorvastatin:
The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin or cytochrome P450 3A4 inhibitors (e.g. cyclosporine, erythromycin, clarithromycin, and azole antifungals).

Grapefruit juice:
Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

Pregnancy
Safety in pregnant women has not been established with AMOSTATIN. AMOSTATIN should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking AMOSTATIN, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers
It is not known whether the amlodipine component of AMOSTATIN is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking AMOSTATIN should not breast-feed.

Pediatric Use
There have been no studies conducted to determine the safety or effectiveness of AMOSTATIN in pediatric populations.

Geriatric Use
There have been no studies conducted to determine the safety or effectiveness of AMOSTATIN in geriatric populations.

ADVERSE REACTIONS

In general, treatment with AMOSTATIN was well tolerated. For the most part, adverse experiences have been mild or moderate in severity. In clinical trials with AMOSTATIN, no adverse experiences peculiar to this combination have been observed. Adverse experiences are similar in terms of nature, severity, and frequency to those reported previously with amlodipine and atorvastatin.
The following information is based on the clinical experience with amlodipine and atorvastatin.

The Amlodipine Component of AMOSTATIN
The following events occurred in <1% but >0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience 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.

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.

Respiratory System: dyspnea,** epistaxis.

Skin and Appendages: angioedema, erythema multiforme, pruritus,** rash,** rash erythematous, rash maculopapular.

**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

The Atorvastatin Component of AMOSTATIN
Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies <2% of patients were discontinued due to adverse experiences attributable to atorvastatin. The most frequent adverse events thought to be related to atorvastatin were constipation, flatulence, dyspepsia, and abdominal pain.

Adverse experiences reported in 2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown below :

Body as a Whole: Chest pain, face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema.

Digestive System: Nausea, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.

Respiratory System: Bronchitis, rhinitis, pneumonia, dyspnea, asthma, epistaxis.

Nervous System: Insomnia, dizziness, paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia.

Musculoskeletal System: Arthritis, leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis.

Skin and Appendages: Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer.

Urogenital System: Urinary tract infection, hematuria, albuminuria, urinary frequency, cystitis, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage.

Special Senses: Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion.

Cardiovascular System: Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension.

Metabolic and Nutritional Disorders: Peripheral edema, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia.

Hemic and Lymphatic System: Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

OVERDOSAGE

There is no information on overdose with AMOSTATIN in humans.

DOSAGE AND ADMINISTRATION

As prescribed by the physician. Dosage of AMOSTATIN must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and hyperlipidemia.

PRESENTATION

AMOSTATIN tablets are available as:
5/10mg in the blister pack of 2 x 10's
5/20mg in the blister pack of 2 x 10's

INSTRUCTIONS:

To be sold on the prescription of a registered medical practitioner only.
Avoid exposure to heat and light.
Store below 30°C.
Keep out of the reach of children.

خوراک:
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔
دوا کو دھوپ اور گرمی سے بچائیں۔
۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
بچوں کی پہنچ سے دور رکھیں۔

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