Amlosterolen (5\20 - 10\40) mg

Company Name:
Medizen Pharmaceutical Industries for Utopia Pharmaceuticals.
Pharmaceutical Form:
Film-coated tablets.
Generic Name:
Amlodipine/atorvastatin(5\20 - 10\40) mg.
Composition:
Each Tablet Contains:
Active Ingredients:
Amlodipine besylate 6.9mg equivalent to 5mg amlodipine + atorvastatin calcium 21.7 mg equivalent to 20 mg atorvastatin or amlodipine besylate 13.87mg equivalent to10mg amlodipine + atorvastatin calcium 43.4mg equivalent to 40mg atorvastatin.
Inactive Ingredients:
Avicel - lactose - stearic acid - povidone k30 - aerosil 200 - croscarmellose sodium - HPMC - PEG - titanium dioxide – talc - FD&C blue.
Pharmacological Action:
Amlosterolen is a combination of two drugs, a dihydropyridine calcium antagonist (long acting Ca-channel blocker) amlodipine (antihypertensive/antianginal agent) and an HMG-CoA reductase inhibitor atorvastatin (cholesterol-lowering agent.)
Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscles and cardiac muscles. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Serum calcium concentration is not affected by amlodipine. 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. **Exertional Angina:** Amlodipine reduces the total peripheral resistance (after load) 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 A_2 analog in human coronary vessels. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.
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), non familial forms of hypercholesterolemia, mixed dyslipidemia and isolated hypertriglyceridemia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.
Pharmacokinetics:
Absorption*:* Following oral administration of Amlosterolen**,** peak plasma concentrations of amlodipine and atorvastatin were seen at 6 to 12 hours and 1 to 2 hours post dosing, respectively. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of Amlosterolen was not affected by food. The absolute bioavailability of atorvastatin is approximately 14%.
Distribution:
Amlodipine: approximately 93% of the circulating amlodipine drug is bound to plasma proteins in hypertensive patients.
Atorvastatin: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is >/= 98% bound to plasma proteins.
Metabolism: Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism. Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products.
Excretion:
Amlodipine: Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. 60% of the metabolites of amlodipine are excreted in the urine.
Atorvastatin: Is eliminated primarily in bile following hepatic and/ or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination

half-life of atorvastatin is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours.

Indications and Usage:

Amlosterolen (amlodipine and atorvastatin) 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 and reduce the risk for revascularization procedures and angina**.** Also, it is indicated in patients with type 2 diabetes without clinically evident coronary heart disease but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension.

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.

3. Elevated Serum TG Levels: Atorvastatin is indicated as an adjunct to diet for the treatment of patients with elevated serum TG levels.

4. Primary Dysbetalipoproteinemia: Atorvastatin is indicated for the treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet.

5. 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.

Dosage and Administration:

Dosage of Amlosterolen must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and hyperlipidemia.

Amlodipine (Hypertension or Angina): The usual initial antihypertensive oral dose of amlodipine is 5 mg once daily with a maximum dose of 10 mg once daily. Dosage should be adjusted according to each patient's need. In general, titration should proceed over 7 to 14 days so that the physician can fully assess the patient's response to each dose level. The recommended dose of amlodipine for chronic stable or vasospastic angina is 5-10 mg, most patients will require 10 mg for adequate effect with the lower dose suggested in the elderly and in patients with hepatic insufficiency. The recommended dose range of amlodipine for patients with coronary artery disease is 5-10 mg once daily.

Atorvastatin (Hyperlipidemia): The recommended starting dose of atorvastatin is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started on 40 mg once daily. Atorvastatin can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of atorvastatin should be individualized according to patient characteristics such as goal of therapy and response. After initiation and/or upon titration of atorvastatin, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly. Dosage adjustment in patients with renal dysfunction is not necessary.

Contraindications:

Amlosterolen contains atorvastatin and is therefore contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases.

Amlosterolen is contraindicated in patients with known hypersensitivity to any component of this medication.

Adverse Reactions:

Amlodipine and atorvastatin: No adverse experiences peculiar to this combination have been observed.

Amlodipine: May cause chest pain, hypotension, tachycardia, peripheral neuropathy, paresthesia, vertigo, anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting**,** allergic arthralgia, arthrosis, muscle cramps, myalgia, dyspnea, epistaxis, erythematous maculopapular rash, micturition disorder, nocturia, hyperglycemia or thirst.

Atorvastatin: Rarely causes face edema, fever, neck rigidity, malaise, photosensitivity reactions,

generalized edema, nausea, gastroenteritis, abnormal liver function tests, colitis, vomiting, gastritis, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice, bronchitis, rhinitis, insomnia, dizziness, paresthesia, amnesia, abnormal dreams, emotional lability, incoordination, peripheral neuropathy, facial paralysis, hyperkinesia, depression, urinary urgency or uterine hemorrhage.

Drug Interactions:

No drug interaction studies have been conducted with Amlosterolen (amlodipine + atorvastatin.) Studies have been conducted in the individual amlodipine and atorvastatin components as described below:

Amlodipine: When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Cimetidine, digoxin, alcohol and warfarin had no significant effects on amlodipine.

Atorvastatin: The risk of myopathy during treatment with drugs of the HMG-CoA reductase class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin or azole antifungals. LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone. When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Plasma concentrations of atorvastatin increased approximately 40% upon coadministration of atorvastatin with erythromycin. Coadministration of atorvastatin and oral contraceptives increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking Amlosterolen. Atorvastatin had no clinically significant effect on warfarin.

LDL-C reduction were not altered by coadministration with antacids, antipyrine or cimetidine.

Pregnancy and Lactation:

Amlosterolen is contraindicated during pregnancy. If the patient becomes pregnant while taking this drug, therapy should be discontinued.

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

Precautions:

- Acute hypotension has rarely been reported after oral administration of amlodipine.
- Calcium channel blockers should be used with caution in patients with heart failure.
- Any withdrawal should be by gradually lowering the dose.
- 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 or cimetidine.

Warnings:

- Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction upon starting calcium channel blocker therapy or at the time of dosage increase.
- It is recommended that liver function tests are to be performed prior to and at 12 weeks following the initiation of therapy, any elevation of dose and periodically.
- Therapy should be temporarily withheld in any patient with myopathy or renal failure secondary to rhabdomyolysis .
- Amlosterolen 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 Amlosterolen.
- Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with the atorvastatin component of Amlosterolen and with other drugs in the HMG-CoA reductase inhibitor class.

Package:

Amlosterolen 5/20 mg: Carton box containing 2 aluminum/aluminum strips plus the insert leaflet. Each strip has 14 film coated tablets.

Amlosterolen 10/40 mg: Carton box containing 2 aluminum/aluminum strips plus the insert leaflet. Each strip has 14 film coated tablets.

Storage:

Keep out of reach of children.

Keep at a temperature not exceeding 30°C in a dry place.

Information for Patients:

- Keep this leaflet. You may need to read it again.
- Follow the physician's instructions.
- Take the dose at the same time every day.
- Do not stop Amlosterolen suddenly.
- Before starting therapy with Amlosterolen, 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**.**

Produced by Medizen Pharmaceutical Industries for Utopia Pharmaceuticals.