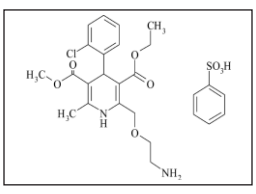
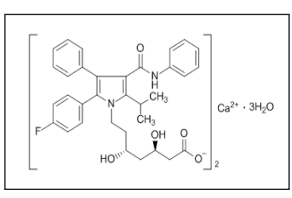
Oscar PLUS Tablets*

آسکر پلس ٹیبلٹس

COMPOSITION:
Each film coated tablet contains: Amlodipine /Atorvastatin ……..... 5/10 mg & 5/20 mg
DESCRIPTION
OSCAR PLUS (amlodipine besylate and atorvastatin calcium) tablets combine the calcium channel blocker amlodipine besylate with the HMG CoA-reductase inhibitor atorvastatin calcium.
Amlodipine besylate: It is chemically described as 3-ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(o-chlorophenyl)-1,4-dihydro6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. Its empirical formula is C20H25ClN2O5C6H6O3S.



Atorvastatin calcium: It is is chemically described as [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. Its empirical formula is (C33H34 FN2O5)2Ca3H2O.



CLINICAL PHARMACOLOGY
Mechanism of Action:
OSCAR PLUS is a combination of two drugs, a dihydropyridine calcium channel blocker (amlodipine) and an HMG-CoA reductase inhibitor (atorvastatin). The amlodipine component of OSCAR PLUS inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The atorvastatin component of OSCAR PLUS 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.
Amlodipine: 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.
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.
Atorvastatin: 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.
Pharmacodynamics:
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.
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.
Atorvastatin
Atorvastatin, as well as some of its metabolites, are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage, rather than systemic drug concentration, correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response.
Pharmacokinetics:
The pharmacokinetic properties of the components of Oscar Plus are provided in Table 1.

Amlodipine	Atorvastatin
Absorption	
After oral administration of therapeutic doses of amlodipine alone, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64% and 90%.	After oral administration alone, atorvastatin is rapidly absorbed; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%.Following oral administration of OSCAR PLUS, peak plasma concentrations of amlodipine and atorvastatin are seen at 6 to 12 hours and 1 to 2 hours post dosing, respectively.
Distribution	
Approximately 93% of the circulating amlodipine drug is bound to plasma proteins in hypertensive patients. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.	Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells.
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. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.
Excretion	
Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Ten percent of the parent amlodipine compound and 60% of the metabolites of amlodipine are excreted in the urine.	Atorvastatin and its metabolites are 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 in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours because of the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

INDICATIONS AND USAGE
OSCAR PLUS (amlodipine and atorvastatin) is indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate.
Hypertension
Amlodipine is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
Coronary Artery Disease (CAD)
- ***Chronic Stable Angina:*** Amlodipine is indicated for the symptomatic treatment of chronic stable angina. Amlodipine may be used alone or in combination with other antianginal 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 agents.
- ***Angiographically Documented:*** CAD In patients with recently documented CAD by angiography and without heart failure or an ejection fraction.
- ***Atorvastatin:*** Therapy with HMG CoA-reductase inhibitors (lipid-altering agents) should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease from hypercholesterolemia. Drug therapy is recommended as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate. In patients with CHD or multiple risk factors for CHD, atorvastatin can be started simultaneously with diet restriction.

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

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 is indicated to:
- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

In patients with clinically evident coronary heart disease, atorvastatin is indicated to:
- Reduce the risk of non-fatal myocardial infarction
- Reduce the risk of fatal and non-fatal stroke
- Reduce the risk for revascularization procedures
- Reduce the risk of hospitalization for CHF
- Reduce the risk of angina

Hyperlipidemia
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 (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and Iib)
As an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV);
For the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet.
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) .
Limitations of Use
Atorvastatin has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (Fredrickson Types I and V).
CONTRAINDICATIONS
Active Liver Disease
Atorvastatin is contraindicated in patients with active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels.
Pregnancy
Atorvastatin is contraindicated in women who are pregnant or may become pregnant. Atorvastatin may cause fetal harm when administered to a pregnant woman.
Nursing Mothers
It is not known whether atorvastatin or amlodipine are excreted into human milk; however, a small amount of another statin does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women taking OSCAR PLUS should not breastfeed their infants.
ADVERSE REACTIONS
The serious adverse reactions is serious symptomatic bradycardia when coadministered with amiodarone. If OSCAR PLUS is administered with ribavirin, refer to the prescribing information for ribavirin for a description of ribavirin-associated adverse reactions. The most common adverse reactions are headache, fatigue, nausea , asthenia, and insomnia and are of mild severity. The most common adverse reactions with ribavirin are fatigue, anemia , nausea, headache, insomnia, and diarrhea .
Laboratory Abnormalities:
- Lipase elevations
- Creatine kinase elevations
- Increases in indirect bilirubin

DRUG INTERACTIONS
No drug interaction studies have been conducted with OSCAR PLUS and other drugs, although studies have been conducted in

the individual amlodipine and atorvastatin components, as described below:

Amlodipine

Impact of Other Drugs on Amlodipine

- **CYP3A Inhibitors**

Co-administration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A inhibitors to determine the need for dose adjustment.

- **CYP3A Inducers**

No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A inducers.

- **Sildenafil**

Monitor for hypotension when sildenafil is co-administered with amlodipine.

Impact of Amlodipine on Other Drugs

- **Immunosuppressants**

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.

Atorvastatin

The risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipidmodifying doses of niacin, cyclosporine, or strong CYP3A4 inhibitors (e.g., clarithromycin, HIV protease inhibitors, and itraconazole).

- **Strong Inhibitors of CYP3A4**

Atorvastatin is metabolized by CYP3A4. Concomitant administration of atorvastatin with strong inhibitors of CYP3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP3A4.

- **Grapefruit Juice**

Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

- **Cyclosporine**

Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day compared to that of atorvastatin alone.The co-administration of atorvastatin with cyclosporine should be avoided.

- **Gemfibrozil**

Because of an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are coadministered with gemfibrozil, avoid concomitant administration of atorvastatin with gemfibrozil.

- **Niacin**

The risk of skeletal muscle effects may be enhanced when atorvastatin is used in combination with niacin; consider a reduction in atorvastatin dosage in this setting.

- **Digoxin**

When multiple doses of atorvastatin and digoxin were co-administered, steady-state plasma digoxin concentrations increased by approximately 20%. Monitor digoxin levels.

- **Oral Contraceptives**

Co-administration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol). Consider these increases when selecting an oral contraceptive for a woman taking OSCAR PLUS .

- **Warfarin**

Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

- **Colchicine**

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine.

USE IN SPECIFIC POPULATION

Pregnancy

Pregnancy Category X

Atorvastatin

It is contraindicated in women who are pregnant or may become pregnant. Atorvastatin may cause fetal harm when administered to a pregnant woman. OSCAR PLUS 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 OSCAR PLUS , it should be discontinued immediately and the patient advised again as to the potential hazards to the fetus, and the lack of known clinical benefit with continued use during pregnancy.

Amlodipine

There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Labor and Delivery

It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while OSCAR PLUS is administered.

Pediatric Use

The safety and effectiveness of OSCAR PLUS have not been established in pediatric populations.

Geriatric Use

Safety and effectiveness of OSCAR PLUS have not been established in geriatric populations.

Hepatic Impairment

OSCAR PLUS is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels.

WARNINGS AND PRECAUTIONS

Myopathy and Rhabdomyolysis

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

The concomitant use of higher doses of atorvastatin with certain drugs such as cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.

Liver Dysfunction

Statins, like atorvastatin, and some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. It is recommended that liver enzyme tests be obtained prior to initiating therapy with atorvastatin and repeated as clinically indicated.

Increased Angina and Myocardial Infarction

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

Hypotension

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

Endocrine Function

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin.

DOSAGE AND ADMINISTRATION

Dosage of OSCAR PLUS must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and hyperlipidemia. Select doses of amlodipine and atorvastatin independently.

OSCAR PLUS may be substituted for its individually titrated components. Patients may be given the equivalent dose of OSCAR PLUS or a dose of OSCAR PLUS with increased amounts of amlodipine, atorvastatin, or both for additional antianginal effects, blood pressure lowering, or lipid-lowering effect. OSCAR PLUS may be used to provide additional therapy for patients already on one of its components. OSCAR PLUS may be used to initiate treatment in patients with hyperlipidemia and either hypertension or angina.

Amlodipine

The usual initial antihypertensive oral dose of amlodipine is 5 mg once daily, and the maximum dose is 10 mg once daily.

Pediatric (age > 6 years), small adult, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding amlodipine to other antihypertensive therapy. Adjust dosage according to blood pressure goals. In general, wait 7 to 14 days between titration steps. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

Angina: The recommended dose of amlodipine for chronic stable or vasospastic angina is 5–10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect.

Coronary artery disease: The recommended dose range of amlodipine for patients with coronary artery disease is 5–10 mg once daily. In clinical studies, the majority of patients required 10 mg.

Pediatrics: The effective antihypertensive oral dose of amlodipine in pediatric patients ages 6–17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients.

Atorvastatin

Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb): 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 at 40 mg once daily. The dosage range of atorvastatin is 10 to 80 mg once daily. Atorvastatin can be administered as a single dose at any time of the day, with or without food.

Homozygous Familial Hypercholesterolemia: The dosage range of atorvastatin in patients with homozygous FH is 10 to 80 mg daily. Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Concomitant Lipid-Lowering Therapy: Atorvastatin may be used with bile acid resins. Monitor for signs of myopathy in patients receiving the combination of HMG-CoA reductase inhibitors (statins) and fibrates.

Patients with Renal Impairment: Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary.

Use with Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors: In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), avoid therapy with atorvastatin. In patients with HIV taking lopinavir plus ritonavir, use the lowest necessary dose of atorvastatin. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, limit therapy with atorvastatin to 20 mg, and make appropriate clinical assessment to ensure that the lowest dose necessary of atorvastatin is employed. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, limit therapy with atorvastatin to 40 mg, and make appropriate clinical assessment to ensure that the lowest dose necessary of atorvastatin is employed.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10–17 years of age): The recommended starting dose of atorvastatin is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more.

OVERDOSAGE

There is no information on overdosage with OSCAR PLUS in humans.

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 overdose should occur with amlodipine, initiate active cardiac and respiratory monitoring. Perform frequent blood pressure measurements.

Atorvastatin

There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Because of extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

STORAGE/PRECAUTIONS: Store in a cool, dry and dark place between 15- 30 °C. Keep all medicines out of the reach of children. To be used on the prescription of Registered Medical Practitioners.

PRESENTATION: OSCAR PLUS Tablets 5/10 mg & 5/20 mg are available in packing containing10 film coated tablets.

***Scotmann Specs.**

خوراک: ڈاکٹر کی ہدایت کے مطابق۔

احتیاط: روشنی، نمی اور گرمی سے بچائیں۔ 15 سے 30 ڈگری سینٹی گریڈ کے درمیان محفوظ کریں۔ تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

مستند ڈاکٹر کے نسخہ پر فروخت اور استعمال کریں۔

Complete Medical Information available only for doctors on request.

scotmann

Manufactured by: **SCOTMANN PHARMACEUTICALS**

5-D, I-10/3 Industrial Area, Islamabad-Pakistan.

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