

Vasclear

(Atorvastatin)

ويسكليئر

COMPOSITION:

Each **Vasclear** 10mg tablet contains atorvastatin calcium trihydrate, equivalent to 10 mg atorvastatin.
Each **Vasclear** 20mg tablet contains atorvastatin calcium trihydrate, equivalent to 20 mg atorvastatin.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Atorvastatin 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. **Vasclear** 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; **Vasclear** also reduces LDL production and the number of LDL particles. **Vasclear** also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1.

PHARMACODYNAMICS

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

Absorption: Atorvastatin is rapidly absorbed after oral administration; 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%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, LDL-C reduction is similar whether atorvastatin is given with or without food. However, LDL-C reduction is the same regardless of the time of day of drug administration.

Distribution: Atorvastatin is ≥98% bound to plasma proteins. Atorvastatin is likely to be secreted in human milk.
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: 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 due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Special Populations

Geriatric: Plasma concentrations of atorvastatin are higher in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults.

Pediatric: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for C_{max} and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with **Vasclear** between men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, 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 since the drug is extensively bound to plasma proteins.

Hepatic Insufficiency: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased.

INDICATIONS

Prevention of Cardiovascular Disease

- In 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.
- 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.
- In patients with clinically evident coronary heart disease.

Hypercholesterolemia

- 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 (eg, LDL apheresis) or if such treatments are unavailable.
- As an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia.

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. After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category. Prior to initiating therapy with **Vasclear**, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. **Vasclear** has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (Fredrickson Types I and V).

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving **Vasclear** and should continue on this diet during treatment with **Vasclear**. Doses should be individualized according to the recommended goal of therapy. After initiation and/or upon titration of **Vasclear**, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly. Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should total-C be used to monitor therapy.

Hypercholesterolemia (Heterozygous Familial & Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa & IIb)

The recommended starting dose of **Vasclear** 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 **Vasclear** is 10 to 80 mg once daily. **Vasclear** can be administered as a single dose at any time of the day, with or without food.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)

The recommended starting dose of **Vasclear** 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).

Homozygous Familial Hypercholesterolemia

The dosage of **Vasclear** in patients with homozygous FH is 10 to 80 mg daily. **Vasclear** 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 Therapy

Vasclear may be used in combination with a bile acid binding resin for additive effect. The combination of HMG-CoA reductase inhibitors and fibrates should generally be avoided.

Dosage in Patients with Renal Insufficiency

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.

UNDESIRABLE EFFECTS

Adverse reactions have usually been mild and transient. Less than 2% of patients were discontinued from clinical trials due to side effects attributed to **Vasclear**.

The most frequent (1% or more) adverse effects associated with **Vasclear** therapy, in patients participating in controlled clinical studies were:

Psychiatric Disorders: insomnia

Nervous System Disorders: headache

Gastrointestinal Disorders: abdominal pain, dyspepsia, nausea, flatulence, constipation, diarrhoea

Musculoskeletal and Connective Tissue Disorders: myalgia

General Disorders: asthenia, elevated serum ALT levels and elevated serum CPK levels

Adverse events that have been reported in atorvastatin clinical trials and in post marketing experience are categorised below according to system organ class and frequency. Frequencies are defined as: very common (>10%), common (>1% and <10%), uncommon (>0.1% and <1%), rare (>0.01% and <0.1%) and very rare (<0.01%).

Gastrointestinal disorders: constipation, flatulence, dyspepsia, nausea, diarrhea, anorexia, vomiting, pancreatitis

Blood and lymphatic system disorders: thrombocytopenia

Immune system disorders: allergic reactions (including anaphylaxis)

Endocrine disorders: alopecia, hyperglycaemia, hypoglycaemia

Psychiatric: insomnia, amnesia

Nervous system disorders: headache, dizziness, paraesthesia, hypoesthesia, peripheral neuropathy, dysgeusia

Eye disorders: visual disturbance

Hepato-biliary disorders: hepatitis, cholestatic jaundice, hepatic failure

Skin/Appendages: skin rash, pruritus, urticaria, alopecia, angioneurotic oedema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis)

Ear and Labyrinth Disorders: tinnitus, hearing loss

Musculoskeletal disorders: myalgia, arthralgia, myopathy, muscle cramps, myositis, rhabdomyolysis, tendon rupture

Reproductive system and breast disorders: impotence, gynecomastia

General disorders: asthenia, chest pain, back pain, fatigue, malaise, weight gain, peripheral oedema

DRUG INTERACTIONS

The risk of myopathy during treatment with drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin and azole antifungals.

Antacid: When atorvastatin and aluminum / magnesium antacid suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered.

Antipyrine: Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Colestipol: Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone.

Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine.

Digoxin: When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4.

Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive 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 atorvastatin.

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

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. 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.

WARNINGS

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 (e.g., semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. 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 atorvastatin is recommended.

Atorvastatin 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 atorvastatin.

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class.

Uncomplicated myalgia has been reported in atorvastatin-treated patients. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Atorvastatin 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

General

Before instituting therapy with atorvastatin, 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.

Pregnancy

Pregnancy Category X

Safety in pregnant women has not been established.

Nursing Mothers

Because of the potential for adverse reactions in nursing infants, women taking **Vasclear** should not breast-feed.

Pediatric Use

Vasclear has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age. Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients.

Geriatric Use

The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (≥65 years of age) was evaluated in the ACCESS study. There were no differences in clinically relevant laboratory abnormalities between the age groups.

Use in Patients with Recent Stroke or TIA

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where **Vasclear** 80 mg vs placebo was administered in 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the **Vasclear** 80 mg group compared to placebo. Subjects with hemorrhagic stroke on study entry appeared to be at increased risk for hemorrhagic stroke.

CONTRAINDICATIONS

- Active liver disease or unexplained persistent elevations of serum transaminases.
- Hypersensitivity to any component of this medication.
- Pregnancy and Lactation

OVERDOSE

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. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

PRESENTATION

Vasclear tablet 10mg: 10's/pack

Vasclear tablet 20mg: 10's/pack

خوراک:

ڈاکٹر کی ہدایت کے مطابق۔

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ہدایت:

دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

دھوپ اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔

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