110 mm

190 mm

avstat-10®

Atorvastatin Tablets 10 mg

COMPOSITION:
Each film coated tablet contains:
Atorvastatin Calcium Trihydrate BP
Equivalent to Atorvastatin 10 mg
Excipients q.s.
Approved colours are used.

PHARMACOLOGICAL CLASSIFICATION: Serum-cholesterol reducers.

PHARMACOLOGICAL ACTION: Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate limiting enzyme that converts 3 hydroxy-3 methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. The liver is its primary site of action and the principal site of cholesterol synthesis and low-density lipoprotein cholesterol (LDL-C) clearance.

In animal models, atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of LDL-C receptors on the cell surface of liver cells, providing for enhanced uptake and catabolism of LDL-C. Atorvastatin reduces LDL-C production and the number of LDL-C particles. Depending on dose, atorvastatin reduces the number of apolipoprotein-B-containing particles in patients with hypercholesterolaemia. Atorvastatin produces a profound and sustained increase in LDL-C receptor activity coupled with a change in the quality of circulating LDL-C particles. Atorvastatin reduces total cholesterol (total-C), LDL-C, apolipoprotein-B in normal volunteers, and in patients with heterozygous familial hypercholesterolaemia, non-familial hypercholesterolaemia, mixed dyslipidaemia, and in some patients with homozygous familial hypercholesterolaemia. It also reduces serum triglycerides (TG) and produces variable increases in high-density lipoprotein cholesterol (HDL-C) and apolipoprotein-A-1 in non-familial hypercholesterolaemia and mixed dyslipidaemias.

Pharmacokinetics and Metabolism:
Absorption: Following oral administration; maximum plasma concentrations occur within 1 to 2 hours. The absolute bioavailability of atorvastatin (parent substance) is approximately 12% 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, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared to morning administration. However, LDL-C reduction is the same regardless of the time of drug administration (see DOSAGE AND DIRECTIONS FOR USE). **Distribution:** Mean volume of distribution of atorvastatin is approximately 381 litres. Atorvastatin is 98% or more bound to plasma proteins. **Metabolism:** Atorvastatin is extensively metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. In vitro inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. **Excretion:** Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism; however, it does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin (parent substance) 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 (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (65 years and older) than in young adults. LDL-C reduction is comparable to that seen in younger patient populations given equal doses of Avstat. **Paediatric:** Pharmacokinetic data in the paediatric population are not available. **Gender:** Plasma concentrations of atorvastatin in women differ (approximately 20% higher for Cmax and 10% lower for AUC) from those in men; however, there is no clinically significant difference in LDL-C reduction with Avstat between men and women. **Race:** Plasma concentrations of atorvastatin are similar in black and white subjects.

INDICATIONS:
Avstat is indicated as an adjunct to diet for reduction of elevated total-cholesterol, LDL-cholesterol, apolipoprotein-B, and triglyceride levels in patients with primary hypercholesterolaemia; mixed dyslipidaemia; and heterozygous familial hypercholesterolaemia.
Avstat is also indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable. Therapy with lipid-lowering agents should be a component of multiple-risk-factor intervention in individuals at increased risk of atherosclerotic vascular disease due to hypercholesterolaemia. 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 non-pharmacological measures has been inadequate. Prior to initiating therapy with Avstat, secondary causes for hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, 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.

CONTRA-INDICATIONS: Hypersensitivity to any component of this medication. Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS and SIDE EFFECTS AND SPECIAL PRECAUTIONS).

Avstat is contra-indicated in pregnancy, in breast feeding mothers and in women of childbearing potential not using adequate contraceptive measures. An interval of one month should be allowed from stopping Avstat treatment to conception in the event of planning a pregnancy.

Children: Safety and efficacy have not yet been established.

WARNINGS:
Liver Effects: Persistent elevations (> 3 times the upper limit of normal (ULN) occurring on 2 or more occasions) in serum transaminases occurred in 0,7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0,2%, 0,2%, 0,6% and 2,3% for 10, 20, 40 and 80 mg respectively. It is recommended that liver function tests be performed before the initiation of treatment, following each dosage increase, and periodically thereafter. Liver enzyme changes mostly commence in the first 4 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,

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withdrawal of atorvastatin is recommended. Avstat 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 contra-indications to the use of Avstat (see CONTRA-INDICATIONS).
Skeletal Muscle Rhabdomyolysis with or without renal impairment has been reported with the use of HMG-CoA reductase inhibitors.
Myalgia has been reported in patients treated with Avstat (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values greater than 10 times the upper limit of normal, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Avstat therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. As with other HMG-CoA reductase inhibitors, the risk of myopathy during treatment with Avstat is increased with concurrent administration of immunosuppressive drugs, including cyclosporine, fibric acid derivatives, nicotinic acid, azole antifungals or erythromycin. (see PRECAUTIONS: Interactions). Avstat therapy should be withdrawn 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, (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

DOSAGE AND DIRECTIONS FOR USE:
The patient should be placed on a standard cholesterol-lowering diet before receiving Avstat and should continue on this diet during treatment with Avstat. The usual starting dose is 10 mg once a day. Doses should be individualised according to the baseline LDL-C levels, the goal of therapy, and patient response. Adjustment of dosage should only be made after an interval of 4 weeks or more. The maximum recommended dose is 40 mg once a day. Doses may be given at any time of day with or without food. Primary Non-familial Hypercholesterolaemia and Combined (Mixed) Hyperlipidaemia The majority of patients are controlled with 10 mg Avstat once a day. A therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 4 weeks. The response is maintained during chronic therapy. Heterozygous Familial Hypercholesterolaemia Patients should be started with Avstat 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, a bile acid sequestrant (e.g. colestipol) may be combined with 40 mg Avstat.
Homozygous Familial Hypercholesterolaemia **Adults:** In a compassionate-use, uncontrolled study of 29 patients with homozygous familial hypercholesterolaemia, most patients responded to a dose of 80 mg of Avstat, with a mean reduction in LDL-C of 20% (range 7% - 53%), although in some patients an increase of LDL-C occurred. **Children:** Treatment experience in the homozygous familial hypercholesterolaemia paediatric population with Avstat is limited. **Dosage in Patients with Renal Insufficiency** Renal disease has no influence on the plasma concentrations nor lipid effects of Avstat; thus, no adjustment of dose is required.
Dosage in Patients with Hepatic Dysfunction In patients with moderate to severe hepatic dysfunction, the therapeutic response to Avstat is unaffected but serum levels of the drug are greatly increased. In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Child-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease. Therefore, caution with dosage should be exercised in patients who consume substantial quantities of alcohol and/or have a history of liver disease. (See CONTRA-INDICATIONS and WARNINGS.)

SIDE-EFFECTS AND SPECIAL PRECAUTIONS: The most frequent adverse effects associated with Avstat therapy, in patients participating in controlled clinical studies were: diarrhoea, constipation, flatulence, dyspepsia, abdominal pain, headache, nausea, myalgia, arthralgia, asthenia, insomnia and rash. The following side-effects have also been reported in clinical trials: muscle cramps, myositis, myopathy, paraesthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, impotence, hyperglycaemia and hypoglycaemia. Allergic reactions have been reported rarely.

Avstat may cause elevation of creatine phosphokinase and dose-related increases in transaminase levels may occur (see WARNINGS). **Interactions:**As with other HMG-CoA reductase inhibitors the risk of myopathy during treatment with Avstat is increased with concurrent administration of immunosuppressive drugs, fibric acid derivatives, macrolide antibiotics, e.g. erythromycin, azole antifungals, e.g. clotrimazole, or niacin (nicotinic acid) (see WARNINGS: Skeletal Muscle). **Antacid:** Co-administration of an oral antacid suspension containing magnesium and aluminium hydroxides with Avstat decreased plasma concentrations of atorvastatin approximately 35%; however, LDL-C reduction was not altered. **Antipyrine:**Because Avstat 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 Avstat were co-administered. However, LDL-C reduction was greater when Avstat and colestipol were co-administered than when either drug was given alone. **Cholestyramine:** No data is available. **Cimetidine:** Atorvastatin plasma concentrations and LDL-C reduction were not altered by co-administration of cimetidine. **Digoxin:** Co-administration of multiple doses of Avstat and digoxin increased steady-state plasma digoxin concentrations by approximately 20%. Patients taking digoxin should be monitored appropriately. **Erythromycin:** In healthy individuals, plasma concentrations of Avstat increased approximately 40% with co-administration of Avstat and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, Skeletal Muscle). **Oral contraceptives:** Co-administration of Avstat and an oral contraceptive increased AUC values of norethindrone and ethinyl estradiol approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin. **Warfarin:** Avstat had no clinically significant effect on prothrombin time when administered to patients receiving combined Avstat and warfarin therapy for two weeks. Nevertheless, patients receiving Avstat should be closely monitored when Avstat is combined with warfarin therapy. **Other Concomitant Therapy:** In clinical studies, Avstat was used concomitantly with antihypertensive agents and oestrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT: 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.

IDENTIFICATION: White elongated film coated tablet, de bossed with 'AT 10' on one side of tablet.

PRESENTATION: 3 strips of 10 tablets each.

STORAGE INSTRUCTIONS: Store below 30°C. Protect from light.

Keep all medicines out of the reach of children.

NAFDAC REG. NO: A4-0271

VSI
Manufactured by: **V. S. International Pvt. Ltd.**
Plot No.: 17&18, Golden Indl. Estate,
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Product Name	**AVSTAT 10**		**Item Code :**	**XXXXXXX**	**Reference Art. :**	**PMA0015**
Packaging Material	**Pack Insert**		**Reason of Change :**	**NEW**	**Specification :**	
Foil Width	**NA**		**Country :**	**NIGERIA**	**GSM**	**60 GSM**
Blister Type	**NA**		**Pack Size :**	**3 x 10's Tablets**	**Board / Paper**	**Maplitho Paper**
Blister Size	**NA**		**Barcode No :**	**NA**	**Varnish Type**	**NA**
Foil Thickness	**NA**		**Pharmacode :**	**NA**	**Grain Direction**	**NA**
Carton Size	**NA**		**Min. Font Size :**	**6 Pt.**	**Braille**	**NA**
Leaflet Size	**110 (L) x 190 (H) mm**		**Language :**	**Eng**	**Finishing Operation**	**NA**
No of Colors : 1	**Black**				**Brand Embossing**	**No**
					Inside Printing	**No**
Remark (if Any) :				**Change Part Layout No. :**		
				Developed For :		
	PREPARED BY	**CHECKED BY**			**APPROVED BY**	**AUTHORISED BY**
SIGNATURE						
DATE						
NAME						
DEPARTMENT	**GRAPHIC DESIGNER**	**PACKING DEV.**	**PACKING DEPT.**	**QUALITY ASSURANCE**	**REGULATORY AFFAIRS**	**QUALITY ASSURANCE**