Sun Pharmaceutical Industries Ltd.
77-B, IFFCO Road, Sector-18,
Gurgaon-122 015 (Haryana), INDIA
Phone : (91-124) 4194200
Fax : (91-124) 4016855
www.sunpharma.com
CIN : L24230GJ1993PLC019050

SUN PHARMA

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

STORVAS

(Atorvastatin Calcium Tablets)

COMPOSITION

STORVAS TABLETS 10 mg
Each film-coated tablet contains:
Atorvastatin Calcium
equivalent to Atorvastatin 10 mg

STORVAS TABLETS 20 mg
Each film-coated tablet contains:
Atorvastatin Calcium
equivalent to Atorvastatin 20 mg

STORVAS TABLETS 40 mg
Each film-coated tablet contains:
Atorvastatin Calcium
equivalent to Atorvastatin 40 mg

STORVAS TABLETS 80 mg
Each film-coated tablet contains:
Atorvastatin Calcium
equivalent to Atorvastatin 80 mg

DESCRIPTION[1]

Atorvastatin calcium is a synthetic lipid-lowering agent. Atorvastatin calcium is chemically designated as [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ - dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). The molecular formula is $(C_{33}H_{34}FN_2O_5)_2Ca$ and its molecular weight is 1155.36.

PHARMACOLOGY[1]

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolised primarily through the high affinity LDL receptor.

Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

Atorvastatin reduces LDL production and the number of LDL particles.

Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles.

Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites (see **PHARMACOKINETICS**).

Atorvastatin has been shown to reduce total-C, LDL-C, apolipoprotein B and triglycerides while producing variable increases in HDL-C in a dose-response study as shown in Table below:

Dose Response in Patients with Primary Hypercholesterolaemia

Atorvastatin Dose (mg)	N	Total C	LDL-C	Apo B	TG	HDL-C
Placebo	12	5	8	6	-1	-2
10	11	-30	-41	-34	-14	4
20	10	-35	-44	-36	-33	12
40	11	-38	-50	-41	-25	-3
80	11	-46	-61	-50	-27	3

Adjusted Mean % change from baseline

Atorvastatin produced a variable but small increase in apolipoprotein AI. However, there was no clear dose response effect.

Review of the current clinical database of 24 complete studies shows that atorvastatin increases HDL-cholesterol and reduces the LDL/HDL and total cholesterol/HDL ratios.

These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.

Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medication. In a compassionate use study, 41 patients aged 6 to 51 years with homozygous familial hypercholesterolaemia or with severe hypercholesterolaemia, who had 15% reduction in LDL-C in response to previous maximum dose combination drug therapy, received daily doses of 40 to 80 mg of atorvastatin. Twenty four patients with homozygous familial hypercholesterolaemia received 80 mg atorvastatin. Nineteen of these 24 patients responded with a greater than 15% reduction of LDL-C (mean 26%, range 18% to 42%).

- **Pharmacokinetics**

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 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.

Mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is ≥98% bound to plasma proteins.

Atorvastatin is 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.

Atorvastatin and atorvastatin metabolites are substrates of P-glycoprotein (see **DRUG INTERACTIONS**). Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the drug does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

Plasma concentrations of atorvastatin are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.

Pharmacokinetic data in the paediatric population are not available.

Concentrations of atorvastatin in women differ (approximately 20% higher for C_{max} and 10% lower for AUC) from those in men. These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin.

Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in C_{max} and 11fold in AUC) in patients with chronic alcoholic liver disease (ChildsPugh B).

INDICATIONS[1]

Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B and triglycerides in patients with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia when response to diet and other nonpharmacological measures is inadequate. Atorvastatin also raises HDL-cholesterol and lowers the LDL/HDL and total cholesterol/HDL ratios.

Atorvastatin is also indicated as an adjunct to diet and other non-dietary measures in reducing elevated total cholesterol, LDL-cholesterol and apolipoprotein B in patients with homozygous familial hypercholesterolaemia when response to these measures is inadequate.

DOSAGE AND ADMINISTRATION[1]

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin and should continue on this diet during treatment with atorvastatin. The usual starting dose is 10 mg once a day. Doses should be individualised according to baseline LDL-C levels, the goal of therapy and patient response. Adjustment of dosage should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day. Doses may be given at any time of day with or without food.

Primary Hypercholesterolaemia and Combined (Mixed) Hyperlipidaemia

The majority of patients are controlled with 10 mg atorvastatin 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.

Current consensus guidelines should be consulted to establish treatment goals for individual patients. The Joint British Recommendations on prevention of coronary heart disease suggest the following targets for lipid management in patients with established coronary heart disease, or other patients at high risk of developing coronary heart disease.

Total cholesterol < 5.0 mmol/L
LDL-cholesterol < 3.0 mmol/L

Heterozygous Familial Hypercholesterolaemia

Patients should be started with atorvastatin 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant (eg., colestipol) may be combined with 40 mg atorvastatin.

Homozygous Familial Hypercholesterolaemia

Adults: In a compassionate-use study of patients with homozygous familial hypercholesterolaemia, most patients responded to a dose of 80 mg of atorvastatin (see **PHARMACOLOGY**).

Children: Treatment experience in a paediatric population with doses of atorvastatin up to 80 mg/day is limited.

Dosage in Patients with Renal Insufficiency

Renal disease has no influence on the plasma concentrations nor lipid effects of atorvastatin; 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 atorvastatin is unaffected but exposure to the drug is greatly increased. C_{max} increases by approximately 16 fold and AUC_{0-24} by approximately 11 fold. Therefore, caution should be exercised in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Geriatric Use

Adequate treatment experience in adults age 70 or older with doses of atorvastatin up to 80 mg/day has been obtained. Efficacy and safety in older patients using recommended doses is similar to that seen in the general population.

PRECAUTIONS[2]

- **General**

Liver Effects: Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality (ies) resolve. Should an increase in ALT or AST of greater than 3 times the upper limit of normal 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.

Creatine phosphokinase measurement: Creatine phosphokinase (CPK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CPK increase as this makes value interpretation difficult. If CPK levels are significantly elevated at baseline (>5 times ULN), levels should be remeasured within 5 to 7 days later to confirm the results.

- **Warnings**

Before treatment: As with other statins atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A creatine phosphokinase (CPK) level should be measured before starting statin treatment in the following situations:

- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- In elderly (age> 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis

In such situations, the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended.

If CPK levels are significantly elevated (>5 times ULN) at baseline, treatment should not be started.

Whilst on treatment:

- If muscular pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CPK levels should be measured. If these levels are found to be significantly elevated (>5 times ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if CPK levels are elevated to ≤ 5 times ULN, treatment discontinuation should be considered.

Sun Pharmaceutical Industries Ltd. Gurgaon 122 015

Supersede: 5059492

Storvas (Front)
PIL size - 140 x 200 mm
Market: Oman
SPIL/PKGDEV - J14/Oct/2014-V01

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- If symptoms resolve and CPK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose with close monitoring.

These CPK elevations should be considered when evaluating the possibility of myocardial infarction in the differential diagnosis of chest pain.
The risk of myopathy during treatment with atorvastatin may be increased with concurrent administration of certain other drugs, such as fibrates (e.g. gemfibrozil) and co-administration should only be undertaken with caution. (see **DRUG INTERACTIONS**).
As with other drugs in this class, rhabdomyolysis with acute renal failure has been reported.
Muscle effects: Treatment with HMG-CoA reductase inhibitors (statins) has been associated with the onset of myalgia, myopathy and very rarely rhabdomyolysis. Myopathy must be considered in any patient under statin therapy presenting with unexplained muscle symptoms such as pain or tenderness, muscle weakness or muscle cramps. In such cases creatine kinase (CK) levels should be measured (see below).

- **Contraindications**

Atorvastatin is contraindicated in patients with hypersensitivity to any component of this medication, active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal, during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures.

- **Pregnancy**

Atorvastatin is contraindicated in pregnancy and while breast-feeding. Women of child-bearing potential should use appropriate contraceptive measures.
An interval of 1 month should be allowed from stopping atorvastatin treatment to conception in the event of planning a pregnancy.

- **Nursing mothers**

In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether this drug or its metabolites is excreted in human milk.

- **Paediatrics**

Data in the paediatric population are not available.

- **Carcinogenicity/ Mutagenicity/ Impairment of Fertility**

Atorvastatin was not carcinogenic in rats. The maximum dose used was 63 fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8 to 16 fold higher based on AUC_{0-24} values as determined by total inhibitory activity. In a 2 year study in mice, incidences of hepatocellular adenoma in males and hepatocellular carcinomas in females were increased at the maximum dose used and the maximum dose used was 250 fold higher than the highest human dose on a mg/kg body-weight basis. Systemic exposure was 6 to 11 fold higher based on AUC_{0-24}. Atorvastatin did not demonstrate mutagenic or clastogenic potential in 4 *in vitro* tests with and without metabolic activation and in 1 *in vivo* assay.
In animal studies atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses foetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to atorvastatin equivalent to 6 and 21 times that expected in man, respectively.

- **Drug Interactions**

The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, azole antifungals, or niacin. This increase in risk may also occur when combining these drugs with atorvastatin.
Antipyrine: Phenazone (antipyrine) is a non-specific model for evaluation of drug metabolism by the hepatic microsomal enzyme system. Administration of multiple doses of atorvastatin with phenazone showed little or no detectable effect on the pharmacokinetics of phenazone in healthy subjects (no change in the clearance of phenazone but the formation clearance of 4-hydroxyphenazone increased by 20% and that of norphenazone by 8%).
More specific *in vitro* studies using human hepatic microsomes and cells expressing human cytochrome P450 isozymes show that atorvastatin, like other HMG-CoA reductase inhibitors, is metabolised by cytochrome P450 3A4 indicating the possibility of an interaction with drugs also metabolised by this isozyme. When combining atorvastatin with other drugs which are the substrate of this isozyme (eg, immunomodulators, many antiarrhythmic agents, some calcium channel antagonists and some benzodiazepines) the possibility of a change in the plasma drug levels of either drug should be considered.
In clinical studies in which atorvastatin was administered with antihypertensives (including ACE inhibitors, beta-blockers, calcium channel antagonists, and diuretics) or hypoglycaemic agents no clinically significant interactions were seen.
Based on experience with other HMG-CoA reductase inhibitors caution should also be exercised when atorvastatin is administered with inhibitors of cytochrome P450 3A4 (eg., certain macrolide antibiotics and azole antifungals). Increases and decreases in plasma phenytoin levels have been reported, but the relationship with atorvastatin is unknown.
Inhibitors of P-glycoprotein: Atorvastatin and atorvastatin-metabolites are substrates of P-glycoprotein. Inhibitors of the P-glycoprotein (e.g. cyclosporin) can increase the bioavailability of atorvastatin and thereby increase the risk of dose-related side-effects such as myopathy.
Gemfibrozil/fibric acid derivatives: The use of fibrates alone is occasionally associated with myopathy. An increased risk of muscle related adverse event has been described when fibrates are co-administered with HMG-CoA reductase inhibitors. The risk of atorvastatin-induced myopathy may therefore be increased with concomitant use of fibric acid derivatives. Pre-clinical data suggest that gemfibrozil may also interact with atorvastatin by inhibiting its glucuronidation. Co-administration of atorvastatin with fibrates (especially gemfibrozil) should only be undertaken with caution.
Digoxin: When multiple doses of digoxin and 10 mg atorvastatin were coadministered, steady state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased approximately 20% following administration of digoxin with 80 mg atorvastatin daily. Patients taking digoxin should be monitored appropriately.
Macrolide antibiotics:
Erythromycin, clarithromycin: Coadministration of atorvastatin and erythromycin (500 mg QID), or clarithromycin (500 mg BID), known inhibitors of cytochrome P450 3A4, were associated with higher plasma concentrations of atorvastatin.
Azithromycin: Coadministration of atorvastatin (10 mg OD) and azithromycin (500 mg OD) did not alter the plasma concentrations of atorvastatin.
Oral contraceptives: Administration of atorvastatin with an oral contraceptive containing norethisterone and ethinyl oestradiol produced increases in plasma concentrations of norethisterone and ethinyl oestradiol. These increased concentrations should be considered when selecting oral contraceptive doses.
Amlodipine: Atorvastatin pharmacokinetics were not altered by the coadministration of atorvastatin 80 mg and amlodipine 10 mg at steady state.
Colestipol: Plasma concentrations of atorvastatin were lower (approximately 25%) when colestipol was administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were administered together than when either drug was given alone.
Antacid: Administration of atorvastatin with an oral antacid suspension containing magnesium and aluminium hydroxides decreased atorvastatin plasma concentrations approximately 35%; however, LDL-C reduction was not altered.
Warfarin: Administration of atorvastatin with warfarin caused a minimal decrease in prothrombin time (mean ± SE of 1.7 ± 0.4 seconds) during the first 4 days of dosing with 80 mg atorvastatin. Dosing continued for 15 days and prothrombin time returned to normal by the end of atorvastatin treatment. Nevertheless, patients receiving warfarin should be closely monitored when atorvastatin is added to their therapy.
Cimetidine: An interaction study with cimetidine and atorvastatin was conducted and no interaction was seen.

- **Adverse Reactions**

Atorvastatin is generally well tolerated. Adverse reactions have usually been mild and transient. Less than 2% of patients were discontinued from clinical trials due to side effects attributed to atorvastatin.
The most frequent (1% or more) adverse effects associated with atorvastatin therapy, in patients participating in controlled clinical studies are constipation, flatulence, dyspepsia, abdominal pain, headache, nausea, myalgia, asthenia, diarrhoea and insomnia. Elevated serum ALT levels have been reported in 1.3% of patients receiving atorvastatin. Clinically important (>3 times upper normal limit) elevations in serum ALT levels occurred in 19 of the 2483 (0.8%) patients on atorvastatin. It was dose related and was reversible in all 19 patients. In 10 cases, the increase was first observed within 12 weeks of starting the treatment. Only 1 case occurred after 36 weeks and only 1 patient had symptoms suggestive of hepatitis. Treatment was discontinued in only 9 of these 19 cases.
Elevated serum CPK levels (>3 times upper normal limit) occurred in 62 of the 2452 (2.5%) patients on atorvastatin compared with 3.1% with other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in only 11 (0.4%) atorvastatin-treated patients. Only 3 (0.1%) of these 11 patients had concurrent muscle pain, tenderness, or weakness.
The following additional adverse effects have been reported in atorvastatin clinical trials: angioneurotic oedema, muscle cramps, myositis, myopathy, paraesthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, rash, impotence, hyperglycaemia, hypoglycaemia, dizziness, chest pain and angina.
Post Marketing Experience
Rare adverse events that have been reported post-marketing that are not listed above are: allergic reactions, (including anaphylaxis and urticaria), bullous skin rashes (including erythema multiforme and Stevens-Johnson syndrome), thrombocytopenia and arthralgia. Rhabdomyolysis has been reported very rarely (see **PRECAUTIONS**).

OVERDOSAGE[1]
Specific treatment is not available for atorvastatin overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests and serum CPK levels should be monitored. Due to extensive drug binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

STORAGE
Store below 25°C, protected from light and moisture.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

SUPPLY
STORVAS 10: Strip of 6's & 10's; Cold form blister of 10's; Carton of 30's and HDPE bottle of 30's
STORVAS 20: Strip of 6's & 10's; Cold form blister of 10's; Carton of 30's and HDPE bottle of 30's
STORVAS 40: Strip of 6's & 10's; Cold form blister of 10's; Carton of 30's and HDPE bottle of 30's
STORVAS 80: Strip of 6's & 10's; Cold form blister of 10's; Carton of 30's and HDPE bottle of 30's

REFERENCE
1. Martindale, The Complete Drug Reference 32nd edn. 1999; 1268.
2. ABPI Compendium of Data Sheets and Summaries of Product Characteristics, *LIPITOR*, Parke Davis Research Laboratories, UK. October 2002.

Information compiled in July' 2004.

Sun Pharmaceutical Industries Ltd. Gurgaon-122015

Manufactured in India by:
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Paonta Sahib, Dist. Sirmour
Himachal Pradesh - 173 025

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