Aw. No.: 20000XXXX

Front

20000XXXX

Atswift 10/20/40/80mg

Atorvastatin Tablets 10mg/20mg/40mg/80mg

COMPOSITION

Atswift Tablet 10mg
Each film coated tablet contains:
Atorvastatin Calcium Trihydrate equivalent to Atorvastatin 10 mg
Excipients q.s.

Atswift Tablet 20mg
Each film coated tablet contains:
Atorvastatin Calcium Trihydrate equivalent to Atorvastatin 20 mg
Excipients q.s.

Atswift Tablet 40mg
Each film coated tablet contains:
Atorvastatin Calcium Trihydrate equivalent to Atorvastatin 40 mg
Excipients q.s.

Atswift Tablet 80mg
Each film coated tablet contains:
Atorvastatin Calcium Trihydrate equivalent to Atorvastatin 80 mg
Excipients q.s.

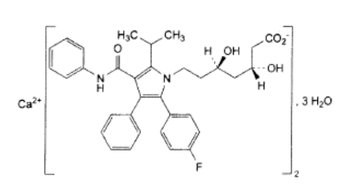
PRODUCT DESCRIPTION:

Atswift Tablet 10 mg:
White colored, oval shaped, biconvex film coated tablets with one side embossed "10" and other side plain.
Atswift Tablet 20 mg:
White colored, oval shaped, biconvex film coated tablets with one side embossed "20" and other side plain.
Atswift Tablet 40 mg:
White colored, oval shaped, biconvex film coated tablets with one side embossed "40" and other side plain.
Atswift Tablet 80 mg:
White colored, oval shaped, biconvex film coated tablets with one side embossed "80" and other side plain.

LIST OF EXCIPIENTS:
Mannitol, Sodium Lauryl Sulfate, Ethanol, Colloidal Anhydrous Silica, Anhydrous Sodium Carbonate, Butylated Hydroxyanisole, Microcrystalline Cellulose, Croscarmellose Sodium, Magnesium Stearate, Sepifilm LP 010 (containing Hypromellose, Microcrystalline Cellulose, Stearic Acid), Purified Water

PRESENTATION:
Atswift Tablet 10 mg: Alu Alu blister pack of 7 Tablets, 4 blister packs per box
Alu Alu blister pack of 10 Tablets, 3 blister packs per box
Alu Alu blister pack of 10 Tablets, 100 blister packs per box
Atswift Tablet 20 mg: Alu Alu blister pack of 7 Tablets, 4 blister packs per box
Alu Alu blister pack of 10 Tablets, 3 blister packs per box
Alu Alu blister pack of 10 Tablets, 100 blister packs per box
Atswift Tablet 40 mg: Alu Alu blister pack of 7 Tablets, 4 blister packs per box
Alu Alu blister pack of 10 Tablets, 3 blister packs per box
Alu Alu blister pack of 10 Tablets, 100 blister packs per box
Atswift Tablet 80 mg: Alu Alu blister pack of 7 Tablets, 4 blister packs per box
Not all presentations may be available locally.

PROPERTIES:
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. Atorvastatin calcium is Calcium (3R5R)-7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoate trihydrate. The empirical formula of atorvastatin calcium is $C_{66}H_{68}CaF_2N_4O_{10}.3H_2O$ and its molecular weight is 1209. Its structural formula is:



CLINICAL PHARMACOLOGY:
PHARMACODYNAMICS:
Pharmacotherapeutic group: Lipid modifying agents, HMG-CoA-reductase inhibitors, ATC code: C10AA05
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 very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the receptor with high affinity to LDL (LDL receptor).
Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis 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. Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medicinal products.
Atorvastatin has been shown to reduce concentrations of total-C (30% - 46%), LDL-C (41% - 61%), apolipoprotein B (34% - 50%), and triglycerides (14% - 33%) while producing variable increases in HDL-C and apolipoprotein A1 in a dose response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.
Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality.

PHARMACOKINETICS AND DRUG METABOLISM
Absorption
Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C_{max}) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. 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
Distribution
Mean volume of distribution of atorvastatin is approximately 381 l. Atorvastatin is ≥98% bound to plasma proteins.
Biotransformation
Atorvastatin is metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized via glucuronidation. 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, atorvastatin 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.
Special populations
Elderly: Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.
Paediatric: In an open-label, 8-week study, Tanner Stage 1 (N=15) and Tanner Stage ≥2 (N=24) paediatric patients (ages 6-17 years) with heterozygous familial hypercholesterolemia and baseline LDL-C ≥ 4 mmol/L were treated with 5 or 10 mg of chewable or 10 or 20 mg of film-coated atorvastatin tablets once daily, respectively. Body weight was the only significant covariate in atorvastatin population PK model. Apparent oral clearance of atorvastatin in paediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC were observed over the range of atorvastatin and o-hydroxyatorvastatin exposures.
Gender: Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for C_{max} and approx. 10% lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.
Renal insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.
Hepatic insufficiency: Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in C_{max} and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B).
SLOC1B1 polymorphism: Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis. Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

Pharmacokinetic Drug Interactions

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC	Change in C_{max}
Glecaprevir 400mg QD/Pibrentasvir 120mg QD, 7 days	10 mg QD for 7 days	↑ 8.3 fold	↑ 22.0 fold
Elbasvir 50mg QD/grazoprevir 200mg QD, 13 days	10 mg single dose	↑ 1.95 fold	↑ 4.3 fold

INDICATIONS AND USAGE:
Hypercholesterolaemia
Atorvastatin Tablets is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate.
Atorvastatin Tablets is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.
Prevention of cardiovascular disease
Atorvastatin Tablets is indicated to reduce the risk of myocardial infarction in adult hypertensive patients without clinically evident coronary heart disease, but with at least three additional risk factors for coronary heart disease such as age ⩾55 years, male sex, smoking, left ventricular hypertrophy, other specified abnormalities on ECG, microalbuminia or proteinuria, ratio of plasma total cholesterol to HDL-cholesterol ⩾6, or premature family history of coronary heart disease.
In adults 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 Tablet is indicated to:
- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
In adults 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

DOSAGE AND ADMINISTRATION:
Posology
The patient should be placed on a standard cholesterol-lowering diet before receiving Atorvastatin Tablets and should continue on this diet during treatment with Atorvastatin Tablets. The dose should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response.
The usual starting dose is 10 mg once a day. Adjustment of dose should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.
Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia
The majority of patients are controlled with Atorvastatin Tablets 10 mg once a day. A therapeutic response is evident within 2 weeks, and the maximum therapeutic response is usually achieved within 4 weeks. The response is maintained during chronic therapy.
Homozygous familial hypercholesterolaemia
In a compassionate-use study of patients with homozygous familial hypercholesterolemia, most patients responded to 80 mg of atorvastatin with a greater than 15% reduction in LDL-C (18%-45%).
Prevention of cardiovascular disease
For primary prevention, the recommended dose is 10 mg once daily. For secondary prevention, optimal dosing may range from 10 mg to 80 mg atorvastatin once daily, to be given at the discretion of the prescriber, taking into account the expected benefit and safety considerations relevant to the patient to be treated
Renal impairment
No adjustment of dose is required.
Hepatic impairment
Atorvastatin Tablets should be used with caution in patients with hepatic impairment. Atorvastatin Tablets is contraindicated in patients with active liver disease.
Use in the elderly
Efficacy and safety in patients older than 70 using recommended doses are similar to those seen in the general population.
Paediatric use
Hypercholesterolaemia:
Paediatric use should only be carried out by physicians experienced in the treatment of paediatric hyperlipidaemia and patients should be re-evaluated on a regular basis to assess progress.
For patients aged 10 years and above, the recommended starting dose of atorvastatin is 10 mg per day with titration up to 20 mg per day. Titration should be conducted according to the individual response and tolerability in paediatric patients. Safety information for paediatric patients treated with doses above 20 mg, corresponding to about 0.5 mg/kg, is limited.
There is limited experience in children between 6-10 years of age. Atorvastatin is not indicated in the treatment of patients below the age of 10 years.
Treatment experience in a pediatric population is limited to doses of atorvastatin up to 80 mg/day for one year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients.
Use in Combination with Other Medicinal Compounds
In cases where co-administration of atorvastatin with cyclosporine, telaprevir, or the combination tipranavir/ritonavir is necessary, the dose of atorvastatin should not exceed 10 mg. Dose of atorvastatin should not exceed 20 mg/day with concomitant use with elbasvir/grazoprevir.
Pharmacokinetic drug interactions that result in increased systemic concentration of atorvastatin have been noted with HIV protease inhibitors (lopinavir plus ritonavir, saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir and nelfinavir), Hepatitis C protease inhibitor (boceprevir), clarithromycin and itraconazole. Caution should be used when co-prescribing atorvastatin and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed.

THE FOLLOWING TREATMENT GUIDELINES MAY BE USED TO ESTABLISH TREATMENT GOALS

A. NCEP (National Cholesterol Education Program) Guidelines for Lipid Management: LDL - C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal mg/dL (mmol/L)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes mg/dL (mmol/L)	LDL Level at Which to Consider Drug Therapy mg/dL(mmol/L)
CHD[a] or CHD risk equivalents (10 - year risk >20%)	<100 (2.6)	≥100 (2.6)	≥130 (3.4) (100 -129: drug optional)[b]
2+ Risk Factors (10 - year risk ≤ 20%)	<130 (3.4)	≥130 (3.4)	10 - year risk 10%-20%: ≥130 (3.4) 10 - year risk <10%: ≥160 (4.1)
0-1 Risk factor[c]	<160 (4.1)	≥160 (4.1)	≥190 (4.9) (160 - 189: LDL-lowering drug optional)

[a] CHD, coronary heart disease.
[b] Some authorities recommend use of LDL -lowering drugs in this category if an LDL C level of <100 mg/dL (2.6 mmol/L) cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
[c] Almost all people with 0 -1 risk factor have 10-year risk <10% ; thus, 10-year risk assessment in people with 0 -1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ⩾200 mg/dL (2.2 mmol/L), non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL (0.8 mmol/L) higher than LDL-C goals for each risk category.

Method of administration
Atorvastatin Tablets is for oral administration. Each daily dose of atorvastatin is given all at once and may be given at any time of day with or without food.

SIDE EFFECTS:
Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 Atorvastatin Tablet vs. 7311 placebo) patients treated for a median period of 53 weeks , 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.
The most frequent (⩾1%) adverse effects that may be associated with atorvastatin therapy, reported in patients participating in placebo-controlled clinical studies include:

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Infections and infestations: nasopharyngitis
Metabolism and nutrition disorders: hyperglycemia
Respiratory, thoracic and mediastinal disorders: pharyngolaryngeal pain, epistaxis
Psychiatric disorders: insomnia
Nervous system disorders: headache
Gastrointestinal disorders: nausea, diarrhea, abdominal pain, dyspepsia, constipation, flatulence
Musculoskeletal and connective tissue disorders: arthralgia, pain in extremity, musculoskeletal pain, muscle spasms, myalgia, joint swelling
General disorders and administration site conditions: asthenia
Investigations: liver function test abnormal, blood creatine phosphokinase increased
Additional adverse effects reported in atorvastatin placebo-controlled clinical trials include:
Metabolism and nutrition disorders: hypoglycemia, hyperglycemia, anorexia
Psychiatric disorders: nightmare
Eye disorders: vision blurred
Ear and labyrinth disorders: tinnitus
Nervous system disorders: peripheral neuropathy, paresthesia
Gastrointestinal disorders: abdominal discomfort, eructation, pancreatitis, vomiting
Hepatobiliary disorders: hepatitis, cholestasis
Skin and subcutaneous tissue disorders: alopecia, pruritus, rash, urticaria
Musculoskeletal and connective tissue disorders: myopathy, myositis, muscle cramps, muscle fatigue, neck pain
Reproductive system and breast disorders: impotence
General disorders and administration site conditions: malaise, pyrexia
Investigations: white blood cells urine positive
Not all effects listed above have been causally associated with atorvastatin therapy.
Paediatric Population
The clinical safety database includes safety data for 249 paediatric patients who received atorvastatin, among which 7 patients were <6 years old, 14 patients were in the age range of 6 to 9, and 228 patients were in the range of 10 to 17.
Nervous system disorders
Common: Headache
Gastrointestinal disorders
Common: Abdominal pain
Investigations: Common: Alanine aminotrasferase increased, blood creatine phosphokinase increased.
Based on the data available, frequency, type and severity of adverse reactions in children are expected to be the same as in adults. There is currently limited experience with respect to long-term safety in the paediatric population.
In post-marketing experience, the following additional undesirable effects have been reported:
Blood and lymphatic system disorders: thrombocytopenia, Immune system disorders: allergic reactions (including anaphylaxis), Injury, poisoning and procedural complications: tendon rupture, Metabolism and nutrition disorders: weight gain, Nervous system disorders: hypoesthesia, amnesia, dizziness, dysgeusia, Gastrointestinal disorders: Pancreatitis, Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, bullous rashes, Musculoskeletal and connective tissue disorders: rhabdomyolysis, immune mediated necrotizing myopathy, back pain, General disorders and Administration site conditions: chest pain, peripheral edema, fatigue.
There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

DRUG INTERACTION AND OTHER FORMS OF INTERACTIONS:
Effect of co-administered medicinal products on atorvastatin
Atorvastatin is metabolized by cytochrome P450 3A4 (CYP3A4) and is a substrate to transport proteins e.g. the hepatic uptake transporter OATP1B1. Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe .
CYP3A4 inhibitors
Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin. Co-administration of potent CYP3A4 inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where co-administration of these medicinal products with atorvastatin cannot be avoided lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended.
Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin. An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been conducted. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.
CYP3A4 inducers
Concomitant administration of atorvastatin with inducers of cytochrome P450 3A (e.g. efavirenz, rifampin, St. John's Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations. The effect of rifampin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.
Transport protein inhibitors
Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in an 8.7- fold increase in atorvastatin AUC. In cases where co-administration of atorvastatin with cyclosporine is necessary, the dose of atorvastatin should not exceed 10 mg.
Atorvastatin is a substrate of the hepatic transporters, OATP1B1 and OATP1B3 transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters MDR1 and BCRP, which may limit the intestinal absorption and biliary clearance of atorvastatin.
Glecaprevir and pibrentasvir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to atorvastatin and concomitant use with atorvastatin is contraindicated.
Elbasvir and grazoprevir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to atorvastatin. Use with caution and lowest dose necessary. Dose of atorvastatin should not exceed 20 mg/day with concomitant use with elbasvir/grazoprevir.
Gemfibrozil / fibric acid derivatives
The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. The risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin. If concomitant administration cannot be avoided, the lowest dose of atorvastatin to achieve the therapeutic objective should be used and the patients should be appropriately monitored.
Ezetimibe
The use of ezetimibe alone is associated with muscle related events, including rhabdomyolysis. The risk of these events may therefore be increased with concomitant use of ezetimibe and atorvastatin. Appropriate clinical monitoring of these patients is recommended.
Colestipol
Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25%) when colestipol was co-administered with Atorvastatin Tablets. However, lipid effects were greater when Atorvastatin Tablets and colestipol were co-administered than when either medicinal product was given alone.
Fusidic acid
Interaction studies with atorvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with atorvastatin and fusidic acid given concurrently. The mechanism of this interaction is not known. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.
Protease inhibitors: Concomitant administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin.
Diltiazem hydrochloride: Co-administration of atorvastatin (40 mg) with diltiazem (240 mg) was associated with higher plasma concentrations of atorvastatin.
Cimetidine: An atorvastatin interaction study with cimetidine was conducted, and no clinically significant interactions were seen.
Itraconazole: Concomitant administration of atorvastatin (20 to 40 mg) and itraconazole (200 mg) was associated with an increase in atorvastatin AUC.
Grapefruit juice: Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).
Antacids: Co-administration of atorvastatin with an oral antacid suspension containing magnesium and aluminum hydroxides, decreased atorvastatin plasma concentrations 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.
Azithromycin: Co-administration of atorvastatin (10 mg once daily) and azithromycin (500 mg once daily) did not alter the plasma concentrations of atorvastatin.
Colchicine: Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.
Amlodipine: In a drug-drug interaction study in healthy subjects, co-adminstration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18% increase in exposure to atorvastatin which was not clinically meaningful.
Effect of atorvastatin on co-administered medicinal products
Digoxin
When multiple doses of digoxin and 10 mg atorvastatin were co-administered, 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.
Oral contraceptives
Co-administration with an oral contraceptive containing norethindrone and ethinyl estradiol 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
In a clinical study in patients receiving chronic warfarin therapy, coadministration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of atorvastatin is changed or discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.
Paediatric population
Drug-drug interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The above mentioned interactions for adults and the warnings should be taken into account for the paediatric population.
Other concomitant therapy: In clinical studies, atorvastatin was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted.

WARNINGS AND PRECAUTIONS:
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 transaminases of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of Atorvastatin Tablets is recommended.
Atorvastatin Tablets should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.
Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)
In a post-hoc analysis of stroke subtypes in patients without coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (TIA) there was a higher incidence of hemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior hemorrhagic stroke or lacunar infarct at study entry. For patients with prior hemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of hemorrhagic stroke should be carefully considered before initiating treatment.
Skeletal muscle effects
Myalgia has been reported in atorvastatin-treated patients. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 x ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. 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, azole antifungals, colchicine, telaprevir, boceprevir or the combination of tipranavir/ritonavir. Many of these drugs inhibit cytochrome P450 3A4 metabolism and/or drug-transport. CYP 3A4 is the primary hepatic isoenzymes known to be involved in the biotransformation of atorvastatin. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Therefore, lower starting and maintenance doses of atorvastatin should also be considered when taken concomitantly with the aforementioned drugs. Temporary suspension of atorvastatin may be appropriate during fusidic acid therapy. 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 may cause an elevation of creatine phosphokinase.
As with other drugs in this class, rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria, have been reported. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects. 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).
Before the treatment
Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK 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
- Situations where an increase in plasma levels may occur, such as interactions and special populations including genetic subpopulations.

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended.
If CK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started.
Creatine kinase measurement
Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (> 5 times ULN), levels should be remeasured within 5 to 7 days later to confirm the results.
Whilst on treatment
- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.
- If such symptoms occur whilst a patient is receiving treatment with atorvastatin, their CK 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 the CK levels are elevated to < 5 x ULN, treatment discontinuation should be considered.
- If symptoms resolve and CK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring. - Atorvastatin must be discontinued if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

Concomitant treatment with other medicinal products
Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, erythromycin, niacin and ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.
In cases where co-administration of these medicinal products with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicinal products that increase the plasma concentration of atorvastatin, a lower maximum dose of atorvastatin is recommended. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended.
The concurrent use of atorvastatin and fusidic acid is not recommended, therefore, temporary suspension of atorvastatin may be considered during fusidic acid therapy.
Paediatric use
Developmental safety in the paediatric population has not been established.
Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.
Hemorrhagic Stroke - A post-hoc analysis of a clinical study in 4,731 patients without CHD who had a stroke or TIA within the preceding 6 months and were initiated on atorvastatin 80 mg, revealed a higher incidence of hemorrhagic stroke in the atorvastatin 80 mg group compared to placebo (55 atorvastatin vs. 33 placebo). Patients with hemorrhagic stroke on entry appeared to be at increased risk for recurrent hemorrhagic stroke (7 atorvastatin vs 2 placebo). The potential risk of hemorrhagic stroke should be carefully considered before initiating treatment with atorvastatin in patients with recent (1-6 months) stroke or TIA.
Endocrine Function - Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin. For some patients, at high risk of diabetes mellitus, hyperglycemia was sufficient to shift them to the diabetes status. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins. Periodic monitoring of these patients is recommended.
Information for the Patient – Patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.
Adolescent females and women of childbearing potential should be counseled on appropriate contraceptive methods while on atorvastatin therapy.

OVERDOSAGE:
Specific treatment is not available for Atorvastatin Tablets overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests should be performed and serum CK levels should be monitored. Due to extensive atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

CONTRAINDICATIONS:
Atorvastatin Tablets is contraindicated in patients:
- with hypersensitivity to the active substance or to any of the excipients of this medicinal product
- with 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.
- Atorvastatin is contraindicated in patients who are concomitantly treated with glecaprevir/pibrentasvir.

STORAGE CONDITION: Store below 30°C. Protect from moisture.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

Manufactured in India by :
Ind-Swift Limited
Village-Jawaharpur,
Off NH-21, Derabassi,
District S.A.S Nagar,
Punjab, India - 140507

Date of revision - September 2020

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Dimension: 200 x 435mm
Paper should be Maplitho (60 GSM)
Font Size : 6 points
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Packaging Development	Marketing	Regulatory Affairs	Production	Quality Control	Quality Assurance	Party Approval