ATORLIP ASP Capsules (Atorvastatin calcium + Aspirin)

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

Qualitative and Quantitative Composition

ATORLIP ASP10

Each capsule contains:

Atorvastatin Calcium equivalent to Atorvastatin …… 10 mg

Aspirin (as gastro-resistant tablet) ……75 mg

ATORLIP ASP20

Each capsule contains:

Atorvastatin Calcium equivalent to Atorvastatin …… 20 mg

Aspirin (as gastro-resistant tablet) ……75 mg

Dosage Form(S) and Strength(S)

Oral capsules of Atorvastatin 10 mg and Aspirin 75 mg

Oral capsules of Atorvastatin 20 mg and Aspirin 75 mg

Clinical Particulars

Therapeutic Indications

ATORLIP ASP (atorvastatin and aspirin) is indicated for the treatment of dyslipidemia associated with artherosclerotic arterial disease with risk of myocardial infarction, stroke or peripheral vascular disease.

Posology and Method of Administration

Patients should be placed on an appropriate lipid-lowering diet before receiving ATORLIP ASP, and should continue this diet during treatment. The recommended dosage is one or two capsules once daily. The dose of atorvastatin can be individualized according to baseline LDL-C levels, the goal of therapy and patient response. The usual starting dose is 10 mg once daily. Adjustment of dose should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once daily. The maximum dose of aspirin in patients with unstable angina pectoris, chronic stable angina pectoris and for prevention of recurrent acute myocardial infarction, ischemic stroke and TIA, CABG, percutaneous transluminal coronary angioplasty PTCA is 325 mg once a day.

Contraindications

- Hypersensitivity to atorvastatin, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), salicylic acid compounds, prostaglandin synthetase inhibitors (e.g. certain asthma patients who may suffer an attack or faint and certain patients who may suffer from bronchospasm, rhinitis and urticaria) or to any of the excipients.
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels
- Active, or history of recurrent peptic ulcer and/or gastric /intestinal hemorrhage or other kinds of bleeding such as cerebrovascular hemorrhages
- Hemorrhagic diathesis, coagulation disorders such as hemophilia and thrombocytopenia
- Patients who are suffering from gout;
- Severe hepatic impairment;
- Methotrexate used at doses >15 mg/week
- Severe renal impairment
- Women who are pregnant or may become pregnant.

    Atorvastatin may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. There are no adequate and well-controlled studies of Atorvastatin use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity. ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, Atorvastatin should be discontinued immediately and the patient apprised of the potential hazard to the fetus.

- Doses >100 mg/day during the third trimester of pregnancy
- Nursing mothers

    It is not known whether atorvastatin is excreted into human milk; however a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require ATORVASTATIN treatment should not breastfeed their infants

Special Warnings and Precautions for Use

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. 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, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN. The concomitant use of higher doses of atorvastatin with certain drugs such as cyclosporine and strong

CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.

Myopathy 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 unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing **ATORLIP ASP**. **ATORLIP ASP** 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, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with **ATORLIP ASP** and fibric acid derivatives, erythromycin, clarithromycin, a combination of ritonavir plus saquinavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or 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. Lower starting and maintenance doses of **ATORLIP ASP** should be considered when taken concomitantly with the aforementioned drugs. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Prescribing recommendations for interacting agents are summarized in Table below.

Table: Drug interactions associated with increased risk of myopathy/rhabdomylosis

Interacting Agents	Prescribing Recommendations
Cyclosporine	Do not exceed 10 mg atorvastatin daily
Clarithromycin, itraconazole, HIV protease inhibitors (ritonavir plus saquinavir or lopinavir plus ritonavir)	Caution when exceeding doses > 20mg atorvastatin daily. The lowest dose necessary should be used.

ATORLIP ASP 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).

Liver Dysfunction

Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Persistent elevations (>3 times the upper limit of normal occurring on two 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.

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations, continued treatment with a

reduced dose of atorvastatin.

It is recommended that liver enzyme tests be obtained 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 **ATORLIP ASP**. 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 **ATORLIP ASP** is recommended.

ATORLIP ASP should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin.

Endocrine Function

Statins 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 statins 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 a statin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone and cimetidine.

Central Nervous System Toxicity

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC(0-24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

Use in Patients with Recent Stroke or Transient Ischemic Attack (TIA)

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where atorvastatin 80 mg versus 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 atorvastatin 80 mg group compared to placebo (55, 2.3% atorvastatin vs. 33, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p = 0.0168). The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 versus 18 for the atorvastatin and

placebo groups, respectively). The incidence of nonfatal hemorrhagic stroke was significantly higher in the atorvastatin group (38, 1.6%) as compared to the placebo group (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the atorvastatin group.

Aspirin

Aspirin is not suitable for use as an antiinflammatory/analgesic/antipyretic.

Recommended for use in adults and adolescents from 16 years of age. This medicinal product is not recommended for use in adolescents/children under 16 years unless the expected benefits outweigh the risks. Acetylsalicylic acid may be a contributory factor in the causation of Reye's Syndrome in some children.

There is an increased risk of haemorrhage particularly during or after operative procedures (even in cases of minor procedures, e.g. tooth extraction). Use with caution before surgery, including tooth extraction. Temporary discontinuation of treatment may be necessary.

Aspirin is not recommended during menorrhagia where it may increase menstrual bleeding.

Aspirin is to be used with caution in cases of hypertension and when patients have a past history of gastric or duodenal ulcer or haemorrhagic episodes or are undergoing therapy with anticoagulants.

Patients should report any unusual bleeding symptoms to their physician. If gastrointestinal bleeding or ulceration occurs the treatment should be withdrawn. Acetylsalicylic acid should be used with caution in patients with moderately impaired renal or hepatic function (contraindicated if severe), or in patients who are dehydrated since the use of NSAIDs may result in deterioration of renal function. Liver function tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency.

Acetylsalicylic acid may promote bronchospasm and asthma attacks or other hypersensitivity reactions. Risk factors are existing asthma, hay fever, nasal polyps or chronic respiratory diseases. The same applies for patients who also show allergic reaction to other substances (e.g. with skin reactions, itching or urticaria).

Serious skin reactions, including Steven-Johnsons syndrome, have rarely been reported in association with the use of acetylsalicylic acid. Aspirin should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including acetylsalicylic acid especially gastrointestinal bleeding and perforation which may be fatal. Where prolonged therapy is required, patients should be reviewed regularly.

Concomitant treatment with Aspirin and other drugs that alter haemostasis (i.e. anticoagulants such as warfarin, thrombolytic and antiplatelet agents, anti-inflammatory drugs and selective serotonin reuptake inhibitors) is not recommended, unless strictly indicated, because they may enhance the risk of haemorrhage. If the combination cannot be avoided, close observation for signs of bleeding is recommended.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration, such as oral corticosteroids, selective serotonin reuptake inhibitors and deferasirox.

Acetylsalicylic acid in low doses reduces uric acid excretion. Due to this fact, patients who tend to have reduced uric acid excretion may experience gout attacks.

The risk of hypoglycaemic effect with sulfonylureas and insulins may be potentiated with Aspirin taken at over dosage.

Aspirin should be avoided in late pregnancy and generally during breast feeding.

Aspirin contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Aspirin contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Drug Interactions

Atorvastatin

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

Strong Inhibitors of CYP3A4: Atorvastatin is metabolized by CYP450 3A4. Concomitant administration of **ATORLIP ASP** with strong inhibitors of CYP3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depends on the variability of effect on CYP3A4.

Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 80 mg with clarithromycin (500 mg twice daily) compared to that of atorvastatin alone. Therefore, in patients taking clarithromycin, caution should be used when the dose of atorvastatin exceeds 20 mg.

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin with ritonavir plus saquinavir (400 mg twice daily) or with lopinavir plus ritonavir (400 mg + 100 mg twice daily), compared to that of atorvastatin alone. Therefore, in patients taking the HIV protease inhibitor caution should be used when prescribing **ATORLIP ASP** and the lowest dose necessary should be used.

Itraconazole: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 40 mg and itraconazole 200 mg. Therefore, in patients taking itraconazole, caution should be used when the atorvastatin dose exceeds 20 mg.

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

Cyclosporine: Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day compared to that of atorvastatin alone. In cases where co-administration of **ATORLIP ASP** with cyclosporine is necessary, the dose of atorvastatin should not exceed 10 mg.

Rifampin or other Inducers of Cytochrome (CY) P450 3A4: Concomitant administration of atorvastatin with inducers of CYP450 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of **ATORLIP ASP** with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

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

Oral Contraceptives: Co-administration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol. These increases should be considered when selecting an oral contraceptive for a woman taking ATORLIP ASP.

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

Aspirin

Contraindicated Combinations

Methotrexate (used at doses >15 mg/week): The combined drugs, methotrexate and acetylsalicylic acid, enhance haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Therefore, the concomitant use of methotrexate (at doses >15 mg/week) with Aspirin is contraindicated.

Not Recommended Combinations

Uricosuric agents, e.g. probenecid: Salicylates reverse the effect of probenecid. The combination should be avoided.

Combinations requiring precautions for use or to be taken into account

Anticoagulants e.g. coumarin, heparin, warfarin and phenindione: Increased risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. The bleeding time should be monitored.

Anti-platelet Agents (e.g clopidogrel and dipyridamole) and selective serotonin re-uptake inhibitors (SSRIs; such as sertraline or paroxetine): Increased risk of gastrointestinal bleeding

Antidiabetics, e.g. Sulphonylureas: Salicylics may increase the hypoglycaemic effect of sulphonylureas

Digoxin and Lithium: Aspirin impairs the renal excretion of lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of lithium is recommended when initiating and terminating treatment with **ATORLIP ASP**. Dose adjustment may be necessary.

Diuretics and Antihypertensives: Aspirin may decrease the antihypertensive effects of diuretics and other antihypertensive agents. As for other aspirin concomitant administration with ACE-inhibitors increases the risk of acute renal insufficiency Diuretics: There is risk of acute renal failure due to decreased glomerular filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is recommended.

Carbonic Anhydrase Inhibitors (Acetazolamide): It may result in severe acidosis and increased central nervous system toxicity.

Systemic Corticosteroids: The risk of gastrointestinal ulceration and bleeding may be increased when acetylsalicylic acid and corticosteroids are co-administered

Methotrexate (used at doses <15 mg/week): The combined drugs, methotrexate and acetylsalicylic acid, may increase haematological toxicity of methotrexate due to decreased renal clearance of methotrexate by acetylsalicylic acid. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly.

Other NSAIDs: Increased risk of ulcerations and gastrointestinal bleeding due to synergistic effects.

Ibuprofen: Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use

Ciclosporin, Tacrolimus: Concomitant administration of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and ATORLIP ASP.

Valproate: Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.

Phenytoin (an antiepileptic): Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered.

Alcohol: Concomitant administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal bleeding.

Antacids will reduce the effect of aspirin. Principle incompatibilities are iron salts, carbonates and alkali hydroxides.

Metamizole: 'Metamizole may reduce the effect of acetylsalicylic acid on platelet aggregation, when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose aspirin for cardioprotection.'

Use in Special Population

Pregnancy:

Pregnancy Category X

Atorvastatin is contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy. Lipid lowering drugs offer no benefit during pregnancy because cholesterol and cholesterol derivatives are needed for normal fetal development. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy.

There are no adequate and well-controlled studies of atorvastatin use during pregnancy. There have been rare reports of congenital anomalies following intrauterine exposure to statins. In a review of about 100 prospectively followed pregnancies in women exposed to other statins, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a three-to-four-fold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2).

In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye-opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day.

Statins may cause fetal harm when administered to a pregnant woman. Atorvastatin should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking Atorvastatin, it should be discontinued immediately and the patient advised again as to the potential hazards to the fetus and the lack of known clinical benefit with continued use during pregnancy.

Nursing Mothers: It is not known whether atorvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Animal breast milk drug levels may not accurately reflect human breast milk levels. Because another drug in this class passes into human milk and because statins have a potential to cause serious adverse reactions in nursing infants, women requiring atorvastatin treatment should be advised not to nurse their infants.

Pediatric Use: Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months' duration in adolescent boys and postmenarchal girls. Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo. The most common adverse experiences observed in both groups, regardless of causality assessment, were infections. Doses greater than 20 mg have not been studied in this patient population. In this limited controlled study, there was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin therapy. Atorvastatin 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: Of the 39,828 patients who received atorvastatin in clinical studies, 15,813 (40%)

were ≥65 years old and 2,800 (7%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older adults cannot be ruled out. Since advanced age (≥65 years) is a predisposing factor for myopathy, atorvastatin should be prescribed with caution in the elderly.

Hepatic Impairment: Atorvastatin is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels.

Effects on the Ability to Drive and Use Machines

None stated

Undesirable Effects

Atorvastatin

The following serious adverse reactions are discussed in greater detail in other sections of the label: Rhabdomyolysis, myopathy and liver enzyme abnormalities

Clinical Trial Adverse Experiences

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the atorvastatin placebo-controlled clinical trial database of 16,066 patients (8,755 atorvastatin versus 7,311 placebo; age range 10 to 93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% other) with a median treatment duration of 53 weeks, 9.7% of patients on atorvastatin and 9.5% of the patients on placebo discontinued due to adverse reactions regardless of causality. The five most common adverse reactions in patients treated with atorvastatin that led to treatment discontinuation and occurred at a rate greater than placebo were myalgia (0.7%), diarrhea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%), and hepatic enzyme increase (0.4%).

The most commonly reported adverse reactions (incidence ≥2% and greater than placebo) regardless of causality, in patients treated with atorvastatin in placebo controlled trials (n=8755) were nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6.0%), and urinary tract infection (5.7%).

Table below summarizes the frequency of clinical adverse reactions, regardless of causality, reported in ≥2% and at a rate greater than placebo in patients treated with atorvastatin (n=8,755), from seventeen placebo-controlled trials.

Table: Clinical adverse reactions occurring in > 2% in patients treated with any dose of Atorvastatin and at an incidence greater than placebo regardless of causality (% of patients)

Adverse Reaction*	Any dose N=8755	10 mg N=3908	20 mg N=188	40 mg N=604	80 mg N=4055	Placebo N=7311	
Nasopharyngitis	8.3	12.9	5.3	7.0	4.2	8.2	
Arthralgia	6.9	8.9	11.7	10.6	4.3	6.5	
Diarrhea	6.8	7.3	6.4	14.1	5.2	6.3	

Pain in extremity	6.0	8.5	3.7	9.3	3.1	5.9	
Urinary tract infection	5.7	6.9	6.4	8.0	4.1	5.6	
Dyspepsia	4.7	5.9	3.2	6.0	3.3	4.3	
Nausea	4.0	3.7	3.7	7.1	3.8	3.5	
Musculoskeletal pain	3.8	5.2	3.2	5.1	2.3	3.6	
Muscle Spasms	3.6	4.6	4.8	5.1	2.4	3.0	
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1	
Insomnia	3.0	2.8	1.1	5.3	2.8	2.9	
Insomnia	2.3	2.9	1.6	2.8	0.7	2.1	
*Adverse reactions ≥2% in any dose greater than placebo							

Other adverse reactions reported in placebo-controlled studies include:

Body as a Whole: malaise, pyrexia

Digestive System: abdominal discomfort, eructation, flatulence, hepatitis, cholestasis

Musculoskeletal System: musculoskeletal pain, muscle fatigue, neck pain, joint swelling

Metabolic and Nutritional System: transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, CPK increase, hyperglycemia

Nervous System: nightmare

Respiratory System: epistaxis

Skin and Appendages: urticaria

Special Senses: vision blurred, tinnitus

Urogenital System: white blood cells urine positive

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)

In ASCOT involving 10,305 participants (age range: 40 to 80 years, 19% women; 94.6% Caucasians, 2.6% Africans, 1.5% South Asians, 1.3% mixed/other) treated with atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

Collaborative Atorvastatin Diabetes Study (CARDS)

In CARDS involving 2,838 subjects (age range: 39 to 77 years, 32% women; 94.3% Caucasians, 2.4% South Asians, 2.3% Afro-Caribbean, 1.0% other) with type 2 diabetes treated with atorvastatin 10 mg daily (n=1,428) or placebo (n=1,410), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported.

Treating to New Targets Study (TNT)

In TNT involving 10,001 subjects (age range: 29 to 78 years, 19% women; 94.1% Caucasians, 2.9%

Blacks, 1.0% Asians, 2.0% other) with clinically evident CHD treated with atorvastatin 10 mg daily (n=5,006) or atorvastatin 80 mg daily (n=4,995), there were more serious adverse reactions and discontinuations due to adverse reactions in the high-dose atorvastatin group (92, 1.8%; 497, 9.9%, respectively) as compared to the low-dose group (69, 1.4%; 404, 8.1%, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations (≥3 × ULN twice within 4 to 10 days) occurred in 62 (1.3%) individuals with atorvastatin 80 mg and in 9 (0.2%) individuals with atorvastatin 10 mg. Elevations of CK (≥10 × ULN) were low overall, but were higher in the high-dose atorvastatin treatment group (13, 0.3%) compared to the lowdose atorvastatin group (6, 0.1%).

Incremental Decrease in Endpoints through Aggressive Lipid Lowering Study (IDEAL)

In IDEAL involving 8,888 subjects (age range 26–80 years, 19% women; 99.3% Caucasians, 0.4% Asians, 0.3% Blacks, 0.04% other) treated with atorvastatin 80 mg/day (n=4439) or simvastatin 20–40 mg daily (n=4449), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 4.8 years.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

In SPARCL involving 4731 subjects (age range 21–92 years, 40% women; 93.3% Caucasians, 3.0% Blacks, 0.6% Asians, 3.1% other) without clinically evident CHD but with a stroke or transient ischemic attack (TIA) within the previous 6 months treated with atorvastatin 80 mg (n=2365) or placebo (n=2366) for a median follow-up of 4.9 years, there was a higher incidence of persistent hepatic transaminase elevations (≥ 3 x ULN twice within 4–10 days) in the atorvastatin group (0.9%) compared to placebo (0.1%). Elevations of CK (>10 x ULN) were rare, but were higher in the atorvastatin group (0.1%) compared to placebo (0.0%). Diabetes was reported as an adverse reaction in 144 subjects (6.1%) in the atorvastatin group and 89 subjects (3.8%) in the placebo group.

In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% versus 274/2366, 11.6%) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% versus 33/2366, 1.4%) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 atorvastatin versus 18 placebo). The incidence of non-fatal hemorrhagic strokes was significantly greater in the atorvastatin group (38 non-fatal hemorrhagic strokes) as compared to the placebo group (16 non-fatal hemorrhagic strokes). Subjects who entered the study with a hemorrhagic stroke appeared to be at increased risk for hemorrhagic stroke.

There were no significant differences between the treatment groups for all-cause mortality: 216 (9.1%) in the atorvastatin 80 mg/day group versus 211 (8.9%) in the placebo group. The proportions of subjects who experienced cardiovascular death were numerically smaller in the atorvastatin 80 mg group (3.3%) than in the placebo group (4.1%). The proportions of subjects who experienced non-cardiovascular death were numerically larger in the atorvastatin 80 mg group (5.0%) than in the placebo group (4.0%).

Post-marketing Experience

The following adverse reactions have been identified during post-approval use of atorvastatin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions associated with atorvastatin therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome,

and toxic epidermal necrolysis), rhabdomyolysis, fatigue, tendon rupture, hepatic failure, dizziness, memory impairment, depression, and peripheral neuropathy.

Pediatric Patients (aged 10 to 17 years)

In a 26-week controlled study in boys and post-menarchal girls (n=140, 31% female; 92% Caucasians, 1.6% Blacks, 1.6% Asians, 4.8% other), the safety and tolerability profile of atorvastatin 10 to 20 mg daily was generally similar to that of placebo.

Aspirin*:*

Blood and lymphatic system disorders:

Common: Increased bleeding tendencies.

Rare: Thrombocytopenia, granulocytosis, aplastic anaemia.

Not known: Cases of bleeding with prolonged bleeding time such as epistaxis, gingival bleeding. Symptoms may persist for a period of 4–8 days after acetylsalicylic acid discontinuation. As a result there may be an increased risk of bleeding during surgical procedures. Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses).

Immune system disorders:

Rare: Hypersensitivity reactions, angio-oedema, allergic oedema, anaphylactic reactions including shock.

Metabolism and digestive system disorders:

Not known: Hyperuricemia.

Nervous system disorders:

Rare: Intracranial haemorrhage

Not known: Headache, vertigo

Ear and labyrinth disorders:

Not known: Reduced hearing ability; tinnitus

Vascular disorders:

Rare: Hemorrhagic vasculitis

Respiratory, thoracic and mediastinal disorders:

Uncommon: Rhinitis, dyspnoea.

Rare: Bronchospasm, asthma attacks

Reproductive system and mammary disorders:

Rare: Menorrhagia

Gastrointestinal disorders:

Common: Dyspepsia.

Rare: Severe gastrointestinal haemorrhage, nausea, vomiting.

Not known: Gastric or duodenal ulcers and perforation, diarrhoea

Hepatobiliary disorders:

Not known: Hepatic insufficiency

Skin and subcutaneous tissue disorders:

Uncommon: Urticaria.

Rare: Steven-Johnsons syndrome, Lyells syndrome, purpura, erythema nodosum, erythema multiforme.

Renal and urinary tract disorders:

Not known: Impaired renal function, salt and water retention

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024. By reporting side-effects, you can help provide more information on the safety of this product.

Overdose

Atorvastatin

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

Aspirin

Although considerable inter-individual variations are involved, it can be considered that the toxic dose is about 200mg/kg in adults and 100mg/kg in children. The lethal dose of acetylsalicylic acid is 25-30 grams. Salicylate poisoning is usually associated with plasma concentrations >300mg/L (2.5 mmol/L). Plasma concentrations above 500mg/l in adults and 300mg/l in children generally cause severe toxicity. Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.

Overdose may harmful for elderly patients and particularly for small children (therapeutic overdose or frequent accidental intoxications may be fatal).

Symptoms of Moderate Intoxications:

Common features of salicylate poisoning include vomiting, nausea, abdominal pain, dehydration,

tinnitus, headache, vertigo, deafness, sweating, warm extremities with bounding pulses.

Symptoms of Severe Intoxications:

Some degree of acid-base disturbance is present in most cases. In the first instance hyperventilation occurs, which results in respiratory alkalosis. Respiratory acidosis ensues due to suppression of the respiratory centre. In addition metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults and children over the age of 4 years as a result of the presence of salicylate. In children aged 4 years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Since younger children are often not seen until they have reached a late stage of intoxication, they are usually in the stage of acidosis.

Furthermore, the following symptoms may occur: haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopaenia, increased INR/PTR, intravascular coagulation, renal failure, non-cardiac pulmonary oedema, hyperthermia and perspiration, resulting in dehydration: feelings of restlessness, convulsions and hallucinations.

Central nervous system features including confusion, disorientation, convulsions may lead to coma, cardiovascular collapse or respiratory arrest are less common in adults than in children.

Treatment of Overdose

If a toxic dose has been ingested, hospital admission is required. In the event of moderate intoxication, inducing the patient to vomit should be attempted.

If this fails, gastric lavage may be attempted during the first hour after ingestion of a substantial amount of the medicine.

Give activated charcoal - (50g for an adult, 1g/kg body weight for a child up to 12 years) - within one hour of ingestion of more than 250 mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate.

The urine pH should be monitored. Correct metabolic acidosis with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema. Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic features. Patients under 10 years or over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

Other symptoms to be treated symptomatically.

Pharmacological Properties

Mechanism of Action

Atorvastatin

Atorvastatin is a selective, competitive inhibitor of 3-hydroxy-3methylglutaryl-coenzyme A (HMG-

CoA) reductase, the rate-limiting enzyme that converts 3-HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides (TG) circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into high-density lipoprotein (HDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) fractions. TG and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C) and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-cholesterol (HDL-C) are associated with a decreased cardiovascular risk.

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 hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles. Atorvastatin reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

Atorvastatin reduces total-C, LDL-C and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia and mixed dyslipidemia. Atorvastatin also reduces VLDL-C and TG and produces variable increases in HDL-C and apo A-1. Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG and non-HDL-C and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin reduces IDL cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched TG-rich lipoproteins, including VLDL, IDL and remnants, can also promote atherosclerosis. Elevated plasma TGs are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD). As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Aspirin

Aspirin is a more potent inhibitor of both prostaglandin synthesis and platelet aggregation than other salicylic acid derivatives. The differences in activity between aspirin and salicylic acid are thought to be due to the acetyl group on the aspirin molecule. This acetyl group is responsible for the inactivation of cyclooxygenase via acetylation. Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclo-oxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet-aggregating factor thromboxane A2.

Non-acetylated salicylates do not inhibit this enzyme and have no effect on platelet aggregation. At somewhat higher doses, aspirin reversibly inhibits the formation of prostaglandin I2 (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation. At higher doses, aspirin is an effective anti-inflammatory agent, partially due to inhibition of inflammatory mediators via cyclo-

oxygenase inhibition in peripheral tissues. In vitro studies suggest that other mediators of inflammation may also be suppressed by aspirin administration, although the precise mechanism of action has not been elucidated.

It is this non-specific suppression of cyclo-oxygenase activity in peripheral tissues following large doses that leads to its primary side effect of gastric irritation.

Pharmacodynamic properties

Atorvastatin

Atorvastatin, as well as some of its metabolites, are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage, rather than systemic drug concentration, correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response.

Aspirin

Pharmacotherapeutic group: Antithrombotic agents: platelet aggregation inhibitors excl. heparin, ATC code: B01AC06.

Aspirin inhibits platelet aggregation. Blocking the platelet cyclooxygenase by acetylation, it inhibits thromboxane A2 synthesis, a physiological activating substance released by the platelets and which would play a role in the complications of the atheromatosic lesions. Inhibition of TXA2-synthesis is irreversible, because thrombocytes, which have no nucleus, are not capable (due to lack of protein synthesis capability) to synthesise new cyclooxygenase, which had been acetylated by acetylsalicylic acid.

The repeated doses from 20 to 325 mg involve an inhibition of the enzymatic activity from 30 to 95%. Due to the irreversible nature of the binding, the effect persists for the lifespan of a thrombocyte (7-10 days). The inhibiting effect does not exhaust during prolonged treatments and the enzymatic activity gradually begins again upon renewal of the platelets 24 to 48 hours after treatment interruption. Acetylsalicylic acid extends bleeding time on average by approximately 50 to 100%, but individual variations can be observed.

Experimental data suggest that Ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of Ibuprofen 400mg was taken within 8 hours before or within 30 minutes after immediate release aspirin (81mg) a decreased effect of aspirin on the formation of thromboxane or platelet aggregation occurred.

However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo, data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

Pharmacokinetic Properties

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. 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 (GI) 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 the C_{max} and area under curve (AUC), LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.

After oral administration, aspirin is rapidly absorbed from the gastrointestinal tract. However, a significant portion of the dosage is already hydrolysed to salicylic acid in the intestinal wall during the absorption process.

Distribution

Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood to plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk.

Acetylsalicylic acid as well as the main metabolite salicylic acid, are extensively bound to plasma proteins, primarily albumin, and distributed rapidly into all parts of the body. Maximum plasma concentration is reached after 0.3 - 2 hours (total salicylate). The volume of distribution of acetylsalicylic acid is ca. 0.16 l/kg of body weight.

Metabolism

Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various betaoxidation 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. In vitro studies suggest the importance of atorvastatin metabolism by CYP450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme. In animals, the orthohydroxy metabolite undergoes further glucuronidation.

Acetylsalicylic acid is rapidly metabolised to salicylic acid, with a half-life of 15-30 minutes. Salicylic acid is subsequently predominantly converted into glycine and glucuronic acid conjugates. Elimination kinetics of salicylic acid is dose dependent, because the metabolism is limited by liver enzyme capacity. Thus, elimination half-time varies and is 2-3 hours after low doses (75 mg – 160 mg).

Elimination

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.

Salicylic acid and its metabolites are predominantly excreted via the kidneys.

Special Populations

Geriatric: Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) 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 atorvastatin between men and women.

Renal Impairment: 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 Impairment: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. C_{max} and AUC are each 4-fold greater in patients with Child-Pugh A disease. C_{max} and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Child-Pugh B disease.

Nonclinical Properties

Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Atorvastatin

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0–24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with Salmonella typhimurium and Escherichia coli, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the in vivo mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100

mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

Aspirin

The nonclinical safety profile of acetylsalicylic acid is well documented.

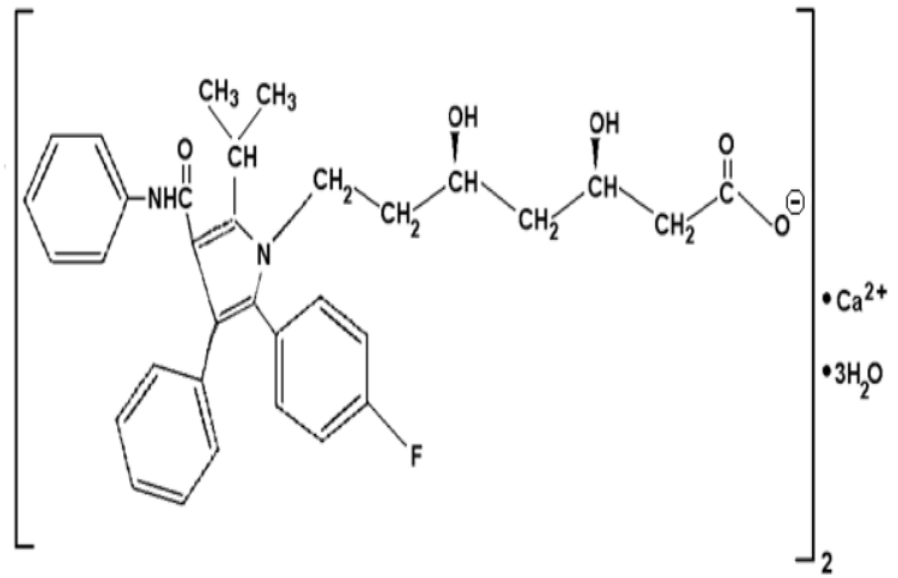
In experimental animal studies, salicylates have shown no other organ injury than renal damage. In rat studies, fetotoxicity and teratogenic effects were observed with acetylsalicylic acid at maternotoxic doses. Clinical relevance is unknown as the doses used in non-clinical studies are much higher (7 times at least) than the maximal recommended doses in targeted cardiovascular indications. Acetylsalicylic acid was extensively investigated with regard to mutagenic and carcinogenic effects. The results as a whole show no relevant signs for any mutagenic or carcinogenic effects in mice and rat studies.

Description

Atorvastatin

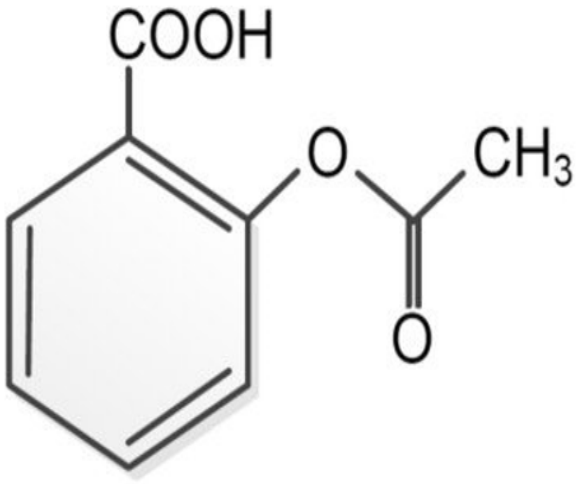
Atorvastatin is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-p-enyl-4-[(phenylamino)carbonyl]-1Hpyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)2Ca•3H_2O$ and its molecular weight is 1209.42. Its structural formula is:



Aspirin

Aspirin, or acetylsalicylic acid (ASA), is commonly used as a pain reliever for minor aches and pains and to reduce fever. It is also an anti-inflammatory drug and can be used as a blood thinner.



Pharmaceutical Particulars

Incompatibilities

None

Shelf-Life

2 years

Packaging Information

ATORLIP ASP10: Strip pack of 10 capsules

ATORLIP ASP20: Strip pack of 10 capsules

Storage and Handling Instructions

Store in a cool, dry place. Protect from light.

Patient Counselling Information

1. **What is ATORLIP ASP?**

ATORLIP ASP is a prescription medicine that lowers cholesterol in your blood. It lowers the LDL-C ("bad" cholesterol) and triglycerides in your blood. It can raise your HDL-C ("good" cholesterol) as well. **ATORLIP ASP** is for adults and children over 10 whose cholesterol does not come down enough with exercise and a low-fat diet alone. **ATORLIP ASP** can lower the risk for heart attack, stroke, certain types of heart surgery, and chest pain in patients who have heart disease or risk factors for heart disease such as:

• age, smoking, high blood pressure, low HDL-C, heart disease in the family. **ATORLIP ASP** can lower the risk for heart attack or stroke in patients with diabetes and risk factors such as:

• eye problems, kidney problems, smoking, or high blood pressure. **ATORLIP ASP** starts to work in about 2 weeks.

Aspirin belongs to a group of medicines called antiplatelet drugs. Platelets are very small structures

in blood, smaller than red or white blood cells, which clump together during blood clotting. By preventing this clumping, antiplatelet drugs reduce the chances of blood clots forming (a process called thrombosis).

1. **Who Should Not Take ATORLIP ASP?**

Do not take **ATORLIP ASP** if you:

- are pregnant or think you may be pregnant or are planning to become pregnant. **ATORLIP ASP** may harm your unborn baby. If you get pregnant, stop taking **ATORLIP ASP** and call your doctor right away.
- are breast feeding. **ATORLIP ASP** can pass into your breast milk and may harm your baby. have liver problems.
- are allergic to **ATORLIP ASP** or any of its ingredients. The active ingredient is atorvastatin.
- See the end of this leaflet for a complete list of ingredients in **ATORLIP ASP** and has not been studied in children under 10 years of age.

- are allergic to ASA, salicylates, non-steroidal anti- inflammatory drugs (NSAIDs)/pain relievers/fever reducers, or other ingredients in the product
- have an ulcer, history of ulcers or are prone to bleeding
- have active or severe liver or kidney disease or congestive heart failure
- have a history of asthma caused by salicylates or other NSAIDs
- are using methotrexate at doses of 15mg/week or more
- are in the last trimester of pregnancy because it may cause problems in the unborn child or complications during delivery

1. **How Should I Take ATORLIP ASP?**

Take **ATORLIP ASP** exactly as prescribed by your doctor. Do not change your dose or stop **ATORLIP ASP** without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during your treatment with **ATORLIP ASP**. Your dose of **ATORLIP ASP** may be changed based on these blood test results.

• Take **ATORLIP ASP** each day at any time of day at about the same time each day. **ATORLIP ASP** can be taken with or without food. Don't break **ATORLIP ASP** tablets before taking.

• Your doctor should start you on a low-fat diet before giving you **ATORLIP ASP**. Stay on this low-fat diet when you take **ATORLIP ASP**.

• If you miss a dose of **ATORLIP ASP**, take it as soon as you remember. Do not take **ATORLIP ASP** if it has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time. Do not take 2 doses of **ATORLIP ASP** at the same time.

• If you take too much **ATORLIP ASP** or overdose, call your doctor or Poison Control Center right away. Or go to the nearest emergency room.

1. **What Should I Avoid While Taking ATORLIP ASP?**

Talk to your doctor before you start any new medicines. This includes prescription and nonprescription medicines, vitamins, and herbal supplements. **ATORLIP ASP** and certain other medicines can interact causing serious side effects.

• Do not get pregnant. If you get pregnant, stop taking **ATORLIP ASP** right away and call your

doctor.

1. **What are the Possible Side Effects of ATORLIP ASP?**

ATORLIP ASP can cause serious side effects. These side effects have happened only to a small number of people. Your doctor can monitor you for them. These side effects usually go away if your dose is lowered or **ATORLIP ASP** is stopped. These serious side effects include:

• Muscle problems.

ATORLIP ASP can cause serious muscle problems that can lead to kidney problems, including kidney failure. You have a higher chance for muscle problems if you are taking certain other medicines with **ATORLIP ASP**.

• Liver problems.

ATORLIP ASP can cause liver problems. Your doctor may do blood tests to check your liver before you start taking **ATORLIP ASP**, and while you take it. Call your doctor right away if you have:

• muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual.

• allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing which may require treatment right away.

• nausea and vomiting.

• passing brown or dark colored urine.

• you feel more tired than usual

• your skin and whites of your eyes get yellow.

• stomach pain.

• allergic skin reactions. In clinical studies, patients reported the following common side effects while taking **ATORLIP ASP**: diarrhea, upset stomach, muscle and joint pain, and alterations in some laboratory blood tests. T

he following additional side effects have been reported with **ATORLIP ASP**: tiredness, and tendon problems. Talk to your doctor or pharmacist if you have side effects that bother you or that will not go away. These are not all the side effects of **ATORLIP ASP**. Ask your doctor or pharmacist for a complete list.

Reporting Side effects

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024. By reporting side-effects, you can help provide more information on the safety of this product.

1. **How do I store ATORLIP ASP?**

Store **ATORLIP ASP** at room temperature, 68 to 77°F (20 to 25°C).

• Do not keep medicine that is out of date or that you no longer need.

• Keep **ATORLIP ASP** and all medicines out of the reach of children. Be sure that if you throw medicine away, it is out of the reach of children.

Details of Manufacturer

Mfg By:

Cipla Ltd

Registered Office: Cipla House,

Peninsula Business Park,

Ganpatrao Kadam Marg

Lower Parel,

Mumbai – 400 013, India

Details of Permission or License Number with Date

M/447/2007

13.09.2015

Date of Revision

31/07/2020