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

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Aspirin Gastro-resistant and Atorvastatin Capsules IP
(Brand Name: LIPONORM®-ASP Capsules)

2. Qualitative and Quantitative Composition

Each Hard Gelatin Capsule Contains:
Aspirin IP ……..……... 75 mg.
(As Aspirin Gastro-resistant Tablets IP)
Colours : Ferric Oxide USP-NF Red & Titanium Dioxide IP
Atorvastatin Calcium IP equivalent to Atorvastatin …… 10 mg.
(As film coated Atorvastatin Tablets IP)
Colours : Titanium Dioxide IP
Approved colours used in hard gelatin capsule shells

3. Dosage Form and Strength

Dosage Form: Capsules.
Dosage Strength: Atorvastatin 10 mg with aspirin 75 mg (as gastro-resistant tablet) per capsule.

4. Clinical Particulars

4.1 Therapeutic Indication

LIPONORM-ASP Capsules are indicated in the following:

- For the primary prevention of coronary artery disease (CAD) in high risk patients.
- For the secondary prevention of transient ischemic attacks (TIAs), stroke and myocardial infarction (MI).
- After percutaneous coronary intervention (PCI).
- Following by-pass surgery/ coronary artery bypass grafting (CABG).

4.2Posology and Method of Administration

For oral administration in adults.
Usual dose is 1 capsule of LIPONORM-ASP to be administered once daily. If required, doses may be increased, but should not exceed the recommended maximum daily doses. Maximum recommended dose of atorvastatin is 80 mg per day while aspirin can be administered up to 300 mg per day.
LIPONORM-ASP Capsules may be preferably administered with food. The capsule should be swallowed whole with water and not be cut, crushed or chewed.

Or, as prescribed by the physician.

4.3Contraindications

LIPONORM-ASP Capsules are contraindicated in the following:

- Hypersensitivity to atorvastatin or to aspirin or to any component of the formulation.
- Severe hepatic impairment, active liver disease, including unexplained persistent elevations in hepatic transaminase levels.
- Coagulation disorders such as hemophilia and thrombocytopenia or concurrent anticoagulant therapy.
- Severe renal impairment.
- Active/history of peptic ulceration and/or GI bleeding.
- Congestive heart failure.
- Patients with a history of asthma induced by NSAIDs (particularly salicylates).
- Patients who are suffering from gout.
- Significant anemia and/or hypothrombinemia.
- Pregnancy.
- Lactation.
- Children.

4.4Special Warnings and Precautions for Use

Atorvastatin

Skeletal Muscle: Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Thus, in such patients, closer monitoring for skeletal muscle effects is required. Atorvastatin, like other statins, occasionally causes myopathy (muscle aches or muscle weakness) in conjunction with increase in creatinine phosphokinase (CPK) values >10 times upper limit of normal (ULN).

Concurrent administration of atorvastatin with certain drugs such as cyclosporine, fibrates, macrolide antibiotics including erythromycin, azole antifungals, HIV-protease inhibitors, or niacin increases the risk of myopathy. On rare occasions, this results in rhabdomyolysis with renal dysfunction secondary to myoglobinuria. In cases where co-administration of these medications with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered.

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 endocrine and electrolyte disorders, and uncontrolled seizures).

Liver Dysfunction: Statins have been associated with biochemical abnormalities of liver function. It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (as clinically indicated) thereafter. There have been rare post-marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. If serious liver injury

with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with atorvastatin, promptly interrupt therapy. If an alternate etiology is not found, do not restart atorvastatin. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications for the use of atorvastatin.

Endocrine Function: Increase in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin. 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. 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.

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 immediately.

Aspirin

Hypersensitivity: Aspirin may precipitate bronchospasm or induce attacks of asthma in susceptible subjects or other hypersensitivity reactions, particularly in individuals with bronchial asthma, hay fever, nasal polyps, or chronic respiratory disease.

Anticoagulant Therapy: Due to its inhibitory effect on platelet aggregation which persists for several days after administration, aspirin may be associated with an increased risk of bleeding. This may occur even during and after surgery (including minor surgeries such as dental extractions). Caution is necessary when LIPONORM-ASP Capsules and anticoagulants are prescribed concurrently, as salicylates can decrease the concentration of prothrombin in the plasma. The dosage of anticoagulant should be adjusted to maintain the Prothrombin Time (PT)/ International Normalized Ratio (INR) at the desired level to prevent bleeding complications.

Peptic Ulcer Disease: Aspirin may cause gastric ulceration and bleeding. Avoid use of aspirin in patients with active peptic ulcer disease.

Fetal Toxicity: Aspirin can cause fetal harm when administered to a pregnant woman. Maternal aspirin use during later stages of pregnancy may cause low birth weight, increased incidence for intracranial hemorrhage in premature infants, stillbirths and neonatal death. Because NSAIDs may cause premature closure of the fetal ductus arteriosus, aspirin should be avoided in the third trimester of pregnancy.

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

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency: Caution should be exercised in patients with G6PD deficiency as hemolytic anemia may occur.

Gout: Aspirin in low doses reduces uric acid excretion. Due to this, patients who tend to have reduced uric acid excretion may experience gout attacks.
Other Precautions: Caution should be exercised in patients with allergic disease, impairment of hepatic or renal function (avoid if severe) and dehydration, since the use of NSAIDs may result in deterioration of renal function.
Chronic Heavy Alcohol Use: Concomitant use of alcohol (three or more drinks per day) and aspirin should be avoided as it increases the risk of GI bleeding.

4.5Drug Interactions

Atorvastatin

CYP3A4 Inhibitors: Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin. Co-administration of potent CYP3A4 inhibitors (e.g., cyclosporine, 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 drugs with atorvastatin cannot be avoided lower starting dose 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. Therefore, a lower dose of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors.
CYP3A4 Inducers: Concomitant administration of atorvastatin with inducers of cytochrome P4503A (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 P4503A 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.
Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor (e.g., telaprevir), compared to that of atorvastatin alone. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of atorvastatin should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing atorvastatin and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of atorvastatin should not exceed 20 mg and should be used with caution. In patients taking the HIV protease inhibitor nelfinavir

or the hepatitis C protease inhibitor boceprevir, the dose of atorvastatin should not exceed 40 mg and close clinical monitoring is recommended.

Grapefruit Juice: Grapefruit juice contains one or more components that inhibit CYP 3A4 and can increase plasma concentration of drugs metabolised by CYP3A4 such as atorvastatin. Intake of 240 ml of grapefruit juice also resulted in a decreased AUC of 20.4% for the active orthohydroxy metabolite. Large quantities of grapefruit juice (> 1.2 liter daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites) HMG-CoA reductase inhibitors 1.3 fold. Thus, concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.

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 atorvastatin.

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

Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported when atorvastatin is co-administered with colchicine, thus, caution should be exercised when prescribing atorvastatin with colchicine.

Niacin: The risk of skeletal muscle effects may be enhanced when atorvastatin is used in combination with niacin. Thus, dosage reduction should be considered in this setting.

Gemfibrozil and Other Fibrates: Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are co-administered with gemfibrozil, concomitant administration of atorvastatin with gemfibrozil should be avoided. Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, atorvastatin should be administered with caution when used concomitantly with other fibrates.

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

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

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.

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. The co-administration of atorvastatin with cyclosporine should be avoided.

Colestipol: Plasma concentrations of atorvastatin and its active metabolites were lower when colestipol was co-administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either drug was given alone.
Fusidic Acid: The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with systemic fusidic acid is necessary, atorvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment.

Aspirin
Methotrexate: Salicylates can inhibit renal clearance (displacing methotrexate from protein binding sites) of methotrexate, leading to bone marrow toxicity, especially in the elderly or renal impaired patients. Therefore, the concomitant use of methotrexate (at doses >15 mg/week) with aspirin is contraindicated.
Uricosuric Agents (Probenecid and Sulfinpyrazone): Salicylates antagonize the uricosuric action of uricosuric agents. Thus, concurrent use of probenecid and sulfinpyrazone with aspirin should be avoided.
Anticoagulants or Trombolytics: Caution is necessary when salicylates and anticoagulants/thrombolytics/other inhibitors of platelet aggregation are prescribed concurrently, as salicylates can reduce the concentration of prothrombin in the plasma, leading to an increased risk of bleeding.
Oral Hypoglycemic Drugs (e.g., Sulfonylureas) / Insulin: Large doses of salicylates have a hypoglycemic action and may enhance the effect of oral hypoglycemic agents. Diabetics receiving concurrent salicylate and hypoglycemic therapy should be monitored closely. Reduction of the hypoglycemic drug dosage may be necessary.
Diuretics: Diuretics in combination with aspirin at higher doses leads to decreased glomerular filtration via decreased prostaglandin synthesis. As a result, sodium excretion may be decreased.
Anticonvulsants: Salicylic acid can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels. Caution is recommended when valproic acid is administered concomitantly with salicylates.
Beta-Blockers: The hypotensive effects of beta-blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.
Systemic Corticosteroids: The risk of GI bleeding and ulceration may be increased when aspirin and corticosteroids are co-administered.
Renin-Angiotensin Aldosterone System (RAAS) Inhibitors: In patients who are elderly, volume-depleted (including those on diuretic therapy), or who have compromised renal function, co-administration of NSAIDs, including aspirin, with RAAS inhibitors may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving RAAS inhibitors and aspirin. NSAIDs, including aspirin, may attenuate the antihypertensive effects of RAAS inhibitors.

Angiotensin Converting Enzyme (ACE) Inhibitors: The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of aspirin due to its indirect effect on the renin-angiotensin conversion pathway (i.e., inhibition of vasodilatory prostaglandins leading to decreased glomerular filtration).
Selective Serotonin Re-uptake Inhibitors (SSRIs): Increased risk of upper GI bleeding due to possibly synergistic effect.
Digoxin: Plasma concentrations of digoxin are increased due to a decrease in renal excretion.
Other NSAIDs: The use of other NSAIDs with salicylates at high doses (≥ 3g/day) may increase the risk of ulcers and GI bleeding due to a synergistic effect. Ibuprofen can interfere with the anti-platelet effect of aspirin. Long-term daily use of ibuprofen may render aspirin less effective when used for cardioprotection and stroke prevention. Nonselective NSAIDs may interfere with the antiplatelet effect of low-dose aspirin.
Carbonic Anhydrase Inhibitors (E.g., Acetazolamide): Salicylate intoxication has occurred in patients on high dose salicylate regimes and carbonic anhydrase inhibitors (reduced excretion of acetazolamide). Concurrent administration of acetazolamide and salicylates may result in severe acidosis and increased central nervous system toxicity.
Antiemetics: Metoclopramide enhances the effects of aspirin by increasing the rate of absorption. Thus, caution is recommended while concomitant use of metoclopramide and aspirin.
Leukotriene Antagonists: Use with caution as the plasma concentration of zafirlukast increases when administered with aspirin.
Antibacterial Agents: The toxicity of sulphonamides may be increased. Caution is recommended while concomitant administration sulphonamides with aspirin.
Cyclosporine, Tacrolimus: Concomitant use of NSAIDs and cyclosporine or tacrolimus may increase the nephrotoxic effect of cyclosporine and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and aspirin.
Thyroid Function Tests: Aspirin may interfere with thyroid function tests.

4.6Use in Special Populations

Pregnant Women

Atorvastatin: Pregnancy Category X; Aspirin: Pregnancy Category C; Aspirin in Third Trimester: Pregnancy Category D. There are no adequate and well-controlled studies of atorvastatin with aspirin combination therapy during pregnancy.
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. There have been rare reports of congenital anomalies following intrauterine exposure to statins. Atorvastatin has the potential to cause hazards to the fetus, thus, it should be administered to women of childbearing potential only when such patients are highly unlikely to conceive. If the woman becomes pregnant while taking atorvastatin, atorvastatin-containing preparation should be discontinued immediately.
When used during the third trimester of pregnancy, non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin may cause premature closure of the fetal ductus arteriosus.

Salicylate products have also been associated with alterations in maternal and neonatal hemostasis mechanisms, decreased birth weight, and with perinatal mortality.
Thus, LIPONORM-ASP Capsules are contraindicated in women who are or may become pregnant.

Lactating Women
LIPONORM-ASP Capsules are contraindicated during breastfeeding. Aspirin is excreted in human milk. There is no available information on the effect of atorvastatin on the breastfed infant or effect on milk production. It is not known whether atorvastatin is excreted in human milk, but a small amount of another drug from the statin class does pass into breast milk. 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. Accordingly, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug therapy to the mother.

Paediatric Patients
Safety and efficacy of this combination therapy has not been established in children and adolescents below 18 years of age. Thus, LIPONORM-ASP Capsules are contraindicated for use in paediatric population.

Geriatric Patients
With atorvastatin and aspirin (when administered separately), no overall differences in safety or effectiveness were observed between geriatric 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. With atorvastatin, advanced age (≥ 65 years) is a predisposing factor for myopathy. With continuous prolonged use of aspirin, elderly patients may be more susceptible to the risk of gastrointestinal (GI) bleeding and perforation which may be fatal. Thus, LIPONORM-ASP Capsules should be prescribed with caution in the elderly patients.

Renal Impairment Patient
LIPONORM-ASP Capsules are contraindicated in patients with severe renal impairment (glomerular filtration rate <10 ml/minute). LIPONORM-ASP Capsules should be used with caution in patients with mild to moderate renal impairment, as use of NSAIDs may result in deterioration of renal function.

Hepatic Impairment Patients
LIPONORM-ASP Capsules are contraindicated in severe hepatic impairment patients and in patients with active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels. LIPONORM-ASP Capsules should be used with caution in patients with mild to moderate hepatic impairment. In these patients, liver function tests should be performed regularly.

4.7Effect on Ability to Drive and Use Machines

Both, atorvastatin and aspirin have negligible influence on the ability to drive and use machines.

4.8Undesirable Effects

Atorvastatin

The two most commonly reported adverse reactions with the use of atorvastatin are:

1. Rhabdomyolysis and myopathy.
2. Liver enzyme abnormalities.

Clinical Trials Experience

The commonly reported adverse reactions (incidence ≥ 2% and greater than placebo) regardless of causality, in patients treated with atorvastatin in placebo-controlled trials were nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6.0%), urinary tract infection (5.7%), dyspepsia (4.7%), nausea (4%), musculoskeletal pain (3.8%), muscle spasm (3.6%), myalgia (3.5%), insomnia (3%), and pharyngolaryngeal pain (2.3%).

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: Increase in transaminases (ALT and AST), abnormal liver function test, increase in blood alkaline phosphatase, increase in creatine phosphokinase, hyperglycemia.

Central Nervous System (CNS): Nightmares.

Respiratory System: Epistaxis.

Skin and Appendages: Urticaria.

Special Senses: Blurred vision, tinnitus.

Urogenital System: Urine test positive for white blood cells (WBCs).

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 include the following: Anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, myositis, fatigue, tendon rupture, fatal and non-fatal hepatic failure, dizziness, depression, peripheral neuropathy, pancreatitis and interstitial lung disease. There have been rare reports of immune-mediated necrotizing myopathy associated with statin use. There has 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).

Aspirin

Following adverse reactions have been reported in patients treated with low dose aspirin:
Gastrointestinal: Nausea, vomiting, diarrhea, GI bleeding and/or ulceration, dyspepsia, heartburn, hematemesis, melena, abdominal pain, and rarely GI inflammation. The frequency and severity of these adverse effects are dose-related.
Ear: Dizziness, tinnitus, vertigo.
Hematologic: Leukopenia, thrombocytopenia, purpura, anemia. Hemolysis and hemolytic anemia in patients with severe forms of G6PD deficiency has been reported.
Dermatologic and Hypersensitivity: Urticaria, pruritus, skin eruptions, asthma, anaphylaxis, edema, nasal congestion, rhinitis.
Central Nervous System: Agitation, cerebral edema, coma, confusion, dizziness, headache, lethargy, seizures.
Fluid and Electrolyte: Hyperkalemia, metabolic acidosis, respiratory alkalosis.
Renal: Interstitial nephritis, papillary necrosis, proteinuria, renal insufficiency and failure.
Miscellaneous: Bleeding, sweating, thirst, transient hepatic impairment.

4.9Overdose

Atorvastatin

An overdose of atorvastatin is not expected to produce life-threatening symptoms. Symptoms of an atorvastatin overdose are unknown. There is no specific treatment for atorvastatin overdose. 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

Salicylate toxicity may result from acute ingestion (overdose) or chronic intoxication. The early signs of salicylic overdose (salicylism), including tinnitus, occur at plasma concentrations approaching 200 mcg/ml. Plasma concentrations of aspirin above 300 mcg/ml are clearly toxic. Severe toxic effects are associated with levels above 400 mcg/ml.
Signs and Symptoms: In acute overdose, severe acid-base and electrolyte disturbances may occur and are complicated by hyperthermia and dehydration. Respiratory alkalosis occurs early while hyperventilation is present, but is quickly followed by metabolic acidosis.
Treatment: Treatment consists primarily of supporting vital functions, increasing salicylate elimination, and correcting the acid-base disturbance. Gastric emptying or lavage is recommended as soon as possible after ingestion, even if the patient has vomited spontaneously. After lavage or emesis, administer activated charcoal, as a slurry, within 3 hours of ingestion.
Severity of aspirin intoxication is determined by measuring the blood salicylate level. Monitor acid-base status with serial blood gas and serum pH measurements. Maintain fluid and electrolyte balance. In severe cases, hyperthermia and hypovolemia are the major

immediate threats to life. Replace fluid intravenously and correct acidosis. Monitor plasma electrolytes and pH to promote alkaline diuresis of salicylate if renal function is normal. Glucose may be required to control hypoglycemia. Hemodialysis and peritoneal dialysis can reduce the body aspirin content. In patients with renal insufficiency or in cases of life-threatening intoxication, dialysis is usually required. Exchange transfusion may be indicated in infants and young children.

5. Pharmacological Properties

5.1 Mechanism of Action

Atorvastatin

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

Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase enzyme and thereby reducing cholesterol biosynthesis in the liver. The liver is the primary site of action and the principal site of cholesterol synthesis and lipoprotein clearance. Atorvastatin reduces low density lipoprotein (LDL) production and the number of LDL particles. Atorvastatin increases the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL.

Aspirin

Aspirin in low doses is used as antiplatelet agent. Chemically, aspirin is acetylsalicylic acid. Aspirin inhibits prostaglandin synthesis resulting in inhibition of platelet aggregation for their lifespan of about 7 to 10 days. The acetyl group of aspirin binds with a serine residue of cyclooxygenase-1 (COX-1), resulting in irreversible inactivation of the enzyme. Inhibition of COX-1 prevents conversion of arachidonic acid to thromboxane A2 (TXA2), which is a potent vasoconstrictor and inducer of platelet aggregation.

5.2Pharmacodynamic Properties

Atorvastatin

Cholesterol and triglycerides (TG) circulate in the bloodstream as part of lipoprotein complexes. Elevated plasma levels of total cholesterol (total-C), low density lipoprotein-cholesterol (LDL-C), and apolipoprotein B (apo B) promote atherosclerosis and are risk factors for developing cardiovascular diseases (CVDs), while increased levels of high density lipoprotein-cholesterol (HDL-C) are associated with a decreased cardiovascular risk.

Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, and TGs and increases HDL-C in patients with hyperlipidemia (heterozygous familial and non-familial) and mixed dyslipidemia (Fredrickson Types IIa and IIb). Therapeutic response of atorvastatin is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

Aspirin

The antiplatelet effect of aspirin is largely unrelated to its systemic bioavailability and its duration of effect does not correlate with the presence of intact salicylic acid in the circulation. The antiplatelet effect is considered to be largely pre-systemic, associated with acetylation of platelet COX in the portal circulation.
With the low dose formulation of aspirin (75 mg gastro-resistant tablets), aspirin is slowly released into the portal circulation and is deacetylated by the liver to inactive salicylate before reaching the systemic circulation. Platelets passing through the portal circulation are exposed to these aspirin in concentrations sufficient to achieve effective thromboxane inhibition.

5.3Pharmacokinetic Properties

Atorvastatin

Absorption: Atorvastatin is rapidly absorbed after oral administration. Maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption, efficacy is similar whether atorvastatin is given with or without food.
Distribution: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins.
Metabolism: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.
Excretion: Atorvastatin 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.

Aspirin

Absorption: Aspirin is rapidly absorbed after oral administration of conventional dosage form. Aspirin undergoes moderate hydrolysis to salicylic acid in the liver and the gastrointestinal wall (before absorption), with 50 to 75% of an administered dose reaching the systemic circulation as intact aspirin. Absorption is delayed in the presence of food. Absorption is more rapid in patients with achlorhydria and also following administration of polysorbates and antacids. The absolute bioavailability of aspirin (75 mg gastro-resistant tablets) compared with intravenous aspirin solution is approximately 25%.
Distribution: Aspirin is poorly bound to plasma proteins and its apparent volume of distribution is low (10 liters). Its metabolite, salicylic acid, is highly bound to plasma proteins, but its binding is concentration-dependent (nonlinear). At low concentrations (< 100

μg/ml), approximately 90% of salicylic acid is bound to albumin. Salicylic acid is widely distributed to all tissues and fluids in the body, including the central nervous system, breast milk, and fetal tissues.

Metabolism: Aspirin is rapidly metabolised to salicylic acid, with a half-life of 15-30 minutes. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide.

Excretion: Aspirin and its metabolites are predominantly excreted via the kidneys. Renal excretion of unchanged drug depends upon urinary pH. As urinary pH rises above 6.5 (alkaline), the rate of excretion of free salicylate increases. Following therapeutic doses, about 10% is excreted as salicylic acid, 75% as salicyluric acid, 10% as the phenolic, and 5% as acyl glucuronides in the urine. Elimination kinetics of salicylic acid is dose-dependent, because the metabolism is limited by liver enzyme capacity. The elimination half-life varies and is 2 to 3 hours after low doses (75 to 160 mg).

6. Nonclinical Properties

6.1 Animal Toxicology

Atorvastatin

Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 *in vitro* tests and 1 *in vivo* assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 folds the $AUC_{0\text{-}24h}$ reached in humans at the highest recommended dose) showed hepatocellular adenomas in males and hepatocellular carcinomas in females.

There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or foetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses foetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk.

Aspirin

No carcinogenesis, mutagenesis or impairment of fertility studies were conducted with aspirin. Aspirin is not considered to be genotoxic or carcinogenic. Studies with oral aspirin in pregnant rats demonstrated the occurrence of fetal malformations at oral doses at or above 250 mg/kg [Human equivalent dose (HED) 40 mg/kg].

A single oral dose of 2500 mg/kg (HED 405 mg/kg) aspirin was well-tolerated in the gastrointestional tract of the rat whereas a single oral dose of aspirin ≥ 740 mg/kg (HED 120 mg/kg) caused lethality and gastric mucosal damage.

7. Description

LIPONORM-ASP Capsules are Opaque White / Opaque White coloured Hard Gelatin Capsule size “1”; containing one white coloured, round, biconvex, both side plain, film

coated tablet (Atorvastatin) and one light brown coloured round, biconvex, enteric coated tablet (Aspirin).

Each capsule of LIPONORM-ASP contains 10 mg of atorvastatin and 75 mg of aspirin (as gastro-resistant tablets) for oral administration in adults.

Atorvastatin Calcium

Atorvastatin calcium is the calcium salt of atorvastatin, a synthetic lipid-lowering agent. Atorvastatin competitively inhibits 3-hydroxy, 3-methylglutaryl-coenzyme A (HMG-CoA) reductase enzyme and thereby reduces cholesterol biosynthesis in the liver.

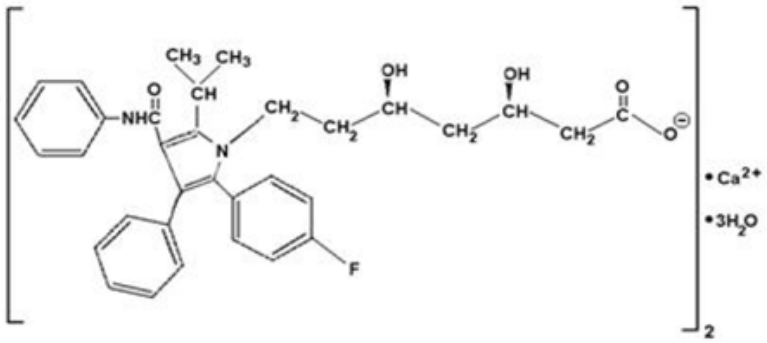
Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol.

Molecular Weight: 1209.42 g/mol.

Molecular Formula: C33H34FN2O5)2Ca•3H2O.

Chemical Name: Calcium;(3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoate;trihydrate.

Structural Formula:



Aspirin

Aspirin is a platelet aggregation inhibitor drug for oral administration. Chemically, aspirin is acetylsalicylic acid.

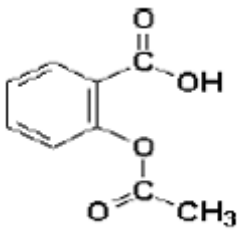
Aspirin is white or almost white crystalline powder or colorless crystals consisting of cubical and squared crystals. It is slightly soluble in water, and soluble in ethanol.

Molecular Weight: 180.16 g/mol.

Molecular Formula: C9H8O4.

Chemical Name: Acetylsalicylic acid or 2-acetyloxybenzoic acid.

Structural Formula:



Inactive ingredients (excipients) of LIPONORM-ASP Capsules contain : Microcrystalline Cellulose, Hydroxy Propyl Cellulose, Hydroxy Propyl Methyl Cellulose, Diethyl Phthalate, Isopropyl Alcohol, Methylene Chloride, Instacoat EN, Lactose, Croscarmellose Sodium, Calcium Carbonate, Polyvinyl Pyrrolidone K – 30, Magnesium Stearate, AKOAT – 512 & Hard Gelatin Capsule.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

18 Months

8.3Packaging Information

15 capsules per strip.

8.4Storage and Handling Instructions

Store protected from moisture, at temperature not exceeding 25°C.
Keep out of reach of children.

9. Patient Counseling Information

- Take LIPONORM-ASP Capsules exactly as prescribed by your doctor. Do not change your dose or stop therapy without talking to your doctor.
- Take LIPONORM-ASP Capsules once daily at any time of day at about the same time each day. LIPONORM-ASP Capsules should be taken with meal. Swallow LIPONORM-ASP capsules whole with water and not to chew or crush them.
- If you miss a dose of LIPONORM-ASP Capsules, take it as soon as you remember. Do not take the drug 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 to make up for a missed dose.
- Do not take LIPONORM-ASP Capsules if you are pregnant or think you may be pregnant, or are planning to become pregnant. Atorvastatin may harm your unborn baby. If you get pregnant, stop taking this medicine and consult your doctor immediately.
- Do not take LIPONORM-ASP Capsules if you are breast feeding. Atorvastatin can pass into your breast milk and may harm your baby.
- Do not take LIPONORM-ASP Capsules if you have kidney and/or liver dysfunction.
- LIPONORM-ASP Capsules are not recommended for use in children.

- Consult your doctor immediately if you suffer from any muscle problems like weakness, tenderness, pain, or more tiredness than usual after taking drug therapy.
- Talk to your doctor before start of any new medication and also inform them about all the medicines that you are taking currently. This includes prescription and nonprescription medicines, vitamins, and herbal supplements. LIPONORM-ASP Capsules and certain other medicines can interact with each other causing serious side effects.
- Do not give LIPONORM-ASP Capsules to other people, even if they have the same problem you have. It may harm them.
- Inform patients that they may bruise or bleed more easily or that it may take longer to stop bleeding. In case of prolonged, unusual, or excessive bleeding, patients to report their doctor. Inform patients to notify their doctor about blood in their stool or urine.
- Advise patients not to take any other NSAID (such as ibuprofen, diclofenac, mefenamic acid, etc.) around the same time of taking LIPONORM-ASP Capsules.

10. Details of Manufacturer

Pure & Cure Healthcare Pvt. Ltd.
(A subsidiary of Akums Drugs & Pharmaceuticals Ltd.)
Plot No. 26A, 27-30, Sector-8A, I.I.E., SIDCUL,
Ranipur, Haridwar – 249 403, Uttarakhand.

11. Details of Permission or License Number with Date

Mfg. Lic. No. : 31/UA/2013. Date of FDA Product Permission:15/12/2021

12. Date of Revision

May 2021.

Marketed by:
EXCEL BLUE CROSS || EXCEL
Division of
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.