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

Atorvastatin and Fenofibrate Tablets IP
(Brand Name: LIPONORM®-F Tablets)

2. Qualitative and Quantitative Composition

Each Film Coated Tablet Contains:
Atorvastatin Calcium IP equivalent to Atorvastatin …… 10 mg.
Fenofibrate IP (micronized) ..…….……..... 160 mg.
Excipients ……. q.s.
Colour : Titanium Dioxide IP

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Atorvastatin 10 mg with fenofibrate 160 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

LIPONORM-F Tablets are indicated for the treatment of mixed dyslipidemia in patients who are not responding adequately to atorvastatin monotherapy, diet and other appropriate measures.

4.2Posology and Method of Administration

For oral administration in adults.
Usual dose is 1 tablet of LIPONORM-F to be administered once daily. After initiation of therapy, lipid levels should be monitored periodically (at 4 to 8 week interval). Dosage should be individualized according to patient response to therapy. Maximum recommended dose of atorvastatin is 80 mg per day while the maximum recommended dose of micronized fenofibrate is 160 mg once daily. If required, higher dose of atorvastatin may be given separately.
LIPONORM-F Tablets should be administered with meal to optimize the absorption of fenofibrate. The tablet should be swallowed whole with water and not to be cut, crushed or chewed.
Or, as prescribed by the physician.

4.3Contraindications

LIPONORM-F Tablets are contraindicated in following conditions:

- Hypersensitivity to atorvastatin or to fenofibrate or to any component of the formulation.
- Patients with active liver disease, including biliary cirrhosis and unexplained persistent liver function abnormalities.
- Severe renal impairment (estimated glomerular filtration rate < 30 ml/min/1.73 m^2), including patients receiving dialysis.
- Pregnancy.
- Lactation.
- Preexisting gall bladder disease.
- Known photo-allergy or phototoxic reaction during treatment with fibrates or ketoprofen.
- Chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridemia.

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.

Fenofibrate

Liver Function: As with other lipid lowering agents, increase in transaminase levels have been reported in some patients when treated with fenofibrate. In the majority of cases these elevations were transient, minor and asymptomatic. It is recommended that transaminase levels be monitored every 3 months during the first 12 months of treatment. Attention should be paid to patients who develop increase in transaminase levels and therapy should be discontinued if AST and ALT levels increase to more than 3 times the upper limit of the normal range or 100 IU.

Pancreatitis: Pancreatitis has been reported in patients taking fenofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation, resulting in the obstruction of the common bile duct.

Skeletal Muscle: Muscle toxicity, including very rare cases of rhabdomyolysis, has been reported with administration of fibrates and other lipid-lowering agents. The incidence of this disorder increases in cases of hypoalbuminemia and previous renal insufficiency. Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscular cramps and weakness and/or marked increases in CPK (levels exceeding 5 times the normal range). In such cases treatment with fenofibrate should be discontinued.

Patients with pre-disposing factors for myopathy and/or rhabdomyolysis, including age above 70 years old, personal or familial history of hereditary muscular disorders, renal impairment, hypothyroidism and high alcohol intake, may be at an increased risk of developing rhabdomyolysis. For these patients, the putative benefits and risks of fenofibrate therapy should be carefully weighed up.

The risk of muscle toxicity may be increased if the drug is administered with another fibrate or an HMG-CoA reductase inhibitor, especially in cases of pre-existing muscular disease. Consequently, the co-prescription of fenofibrate with a statin should be reserved for patients with severe combined dyslipidemia and high cardiovascular risk without any history of muscular disease. This combination therapy should be used with caution and patients should be monitored closely for signs of muscle toxicity.

Renal Function: Fenofibrate is contraindicated in severe renal impairment. Fenofibrate should be used with caution in patients with mild to moderate renal insufficiency. Dose should be adjusted in patients whose estimated glomerular filtration rate is 30 to 59 ml/min/1.73 m^2. Reversible elevations in serum creatinine have been reported in patients receiving fenofibrate monotherapy or co-administered with statins. Elevations in serum creatinine were generally stable over time with no evidence for continued increases in serum creatinine with long-term therapy and tended to return to baseline following discontinuation of treatment. Treatment should be interrupted when creatinine level is 50% above the upper limit of normal. It is recommended that creatinine be measured during the first 3 months after initiation of treatment and periodically thereafter.

Cholelithiasis: Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Fenofibrate therapy should be discontinued if gallstones are found.

Coumarin Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with fenofibrate because of the potentiation of coumarin-type anti-coagulant effects in prolonging the prothrombin time/International Normalized Ratio (PT/INR). The dosage of the anticoagulant should be reduced to maintain the PT/INR at the desired level to prevent bleeding complications. Frequent PT/INR determinations are advisable until it has been definitely determined that the PT/INR has stabilized.

Hematologic Changes: Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Thrombocytopenia and agranulocytosis have been reported in individuals treated with fenofibrate. Periodic monitoring of red and white cell counts is recommended during the first 12 months of fenofibrate administration.

Hypersensitivity Reactions: Acute hypersensitivity reactions such as Stevens-Johnson syndrome, and toxic epidermal necrolysis requiring patient hospitalization and treatment with steroids have been reported in individuals treated with fenofibrates.

Paradoxical Decrease in HDL-Cholesterol Levels: There have been post-marketing and clinical trial reports of severe decreases in HDL-C levels (as low as 2 mg/dl) occurring in diabetic and non-diabetic patients initiated on fibrate therapy. The decrease in HDL-C is mirrored by a decrease in apolipoprotein A1. This decrease has been reported to occur within 2 weeks to years after initiation of fibrate therapy. The HDL-C levels remain depressed until fibrate therapy has been withdrawn; the response to withdrawal of fibrate therapy is rapid and sustained. The clinical significance of this decrease in HDL-C is unknown. It is recommended that the HDL-C levels be checked within the first few months after initiation of fibrate therapy. If a severely decreased HDL-C level is detected, fibrate therapy should be withdrawn, and the HDL-C level monitored until it has returned to baseline. Fibrate therapy should not be re-initiated in such cases.

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.

Fenofibrate

Oral Anticoagulants: Fenofibrate enhances oral anticoagulant effect and may increase risk of bleeding. Thus, caution should be exercised when coumarin anticoagulants are administered in conjunction with fenofibrate. It is recommended that the dosage of the anticoagulants be reduced to maintain the PT/INR at the desired level to prevent bleeding

complications. Frequent PT/INR determinations are advisable until it has been determined with certainty that the PT/INR has stabilized.

Immunosuppressants: Immunosuppressants such as cyclosporine and tacrolimus can produce nephrotoxicity with decreases in creatinine clearance and rise in serum creatinine levels. Because renal excretion is the primary elimination route of fibrate drugs including fenofibrate, there is a risk that an interaction will lead to deterioration of renal function. The benefits and risks of using fenofibrate with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed and renal function be closely monitored. In the case of severe alteration of laboratory parameters, treatment with fenofibrate should be stopped.

Bile-Acid Binding Resins: Since bile acid resins may bind other drugs given concurrently, fenofibrate should be taken at least 1 hour before or 4 to 6 hours after a bile acid binding resin to avoid impeding its absorption.

Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported when fenofibrate co-administered with colchicine. Thus, caution should be exercised when fenofibrate is given with colchicine.

Statins and Other Fibrates: The risk of serious muscle toxicity increased if fenofibrate is used concomitantly with HMG-CoA reductase inhibitors/statins or other fibrates. Such combination therapy should be used with caution and patients monitored closely for signs of muscle toxicity.

Cytochrome P450 Enzymes: *In vitro* studies using human liver microsomes indicate that fenofibrate and fenofibric acid is not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations. Patients co-administered fenofibrate and CYP2C19, CYP2A6, and especially CYP2C9- metabolised drugs with a narrow therapeutic index should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

4.6Use in Special Populations

Pregnant Women

Atorvastatin - Pregnancy Category X. Fenofibrate - Pregnancy Category C. There are no adequate and well-controlled studies of this combination therapy in pregnant women. LIPONORM-F Tablets are 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. 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, the atorvastatin-containing preparation should be discontinued immediately. Atorvastatin may cause fetal harm when administered to a pregnant woman. Females of reproductive potential are advised to use effective contraception during treatment with atorvastatin.

Safety of fenofibrate in pregnant women has not been established. There are no adequate and well controlled studies of fenofibrate in pregnant women. Animal studies have not demonstrated any teratogenic effects. Embryotoxic effects have been shown at doses in the range of maternal toxicity. The potential risk for humans is unknown. Therefore, fenofibrate should only be used after a careful benefit/risk assessment.

Lactating Women

LIPONORM-F Tablets are contraindicated during breastfeeding. There are no data on the excretion of fenofibrate and/or its metabolites into breast milk. Fenofibrate should not be used in nursing mothers. 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 to the mother.

Paediatric Patients

Safety and efficacy of atorvastatin with fenofibrate combination therapy has not been established in paediatric patients. Thus, LIPONORM-F Tablets are not recommended in children and adolescents below 18 years of age.

Geriatric Patients

Elderly patients with normal renal function may be given the same dose as recommended for adults; no dosage modification is required in these patients.

With atorvastatin, 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. However, with atorvastatin therapy, advanced age (≥65 years) is a predisposing factor for myopathy.

Fenofibric acid exposure is not influenced by age. Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Since elderly patients have a higher incidence of renal impairment, dose selection for the elderly should be made on the basis of renal function.

Since impairment of renal function is more common in the elderly patients and they are at higher risk of having atorvastatin-associated myopathy, LIPONORM-F Tablets should be used with caution in the elderly population. Also, it is recommended to monitor renal function regularly.

Renal Impairment Patient

Renal disease does not affect the plasma concentrations of atorvastatin. However, fenofibrate is primarily excreted by the kidney. Patients with severe renal impairment have 2.7-fold higher exposure of fenofibric acid and increased accumulation of fenofibric acid during chronic dosing compared with healthy volunteers. Thus, LIPONORM-F Tablets are

contraindicated in patients with severe renal impairment, including those with end-stage renal disease (ESRD) and those receiving dialysis. In addition, avoid use in patients with mild or moderate renal impairment. If used in these patients, dose reduction is required and monitoring of renal function is recommended.

Hepatic Impairment Patients

The use of fenofibrate has not been evaluated in subjects with hepatic impairment. Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism. Thus, atorvastatin-containing preparations should be used with caution in patients with hepatic impairment. LIPONORM-F Tablets are contraindicated in patients with active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels.

4.7Effect on Ability to Drive and Use Machines

Both, atorvastatin and fenofibrate 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:

- Rhabdomyolysis and myopathy.
- 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.
- Nervous System: 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).

Fenofibrate

Clinical Trials Experience

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

Adverse reactions reported by 2% or more of patients treated with fenofibrate and greater than placebo during double-blind, placebo-controlled trials are: Abdominal pain, back pain, headache, nausea, constipation, abnormal liver function tests, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased creatine phosphokinase (CPK), respiratory disorders, rhinitis.

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of fenofibrate: Myalgia, rhabdomyolysis, pancreatitis, muscle spasms, acute renal failure, hepatitis, cirrhosis, anemia, arthralgia, asthenia, and very low HDL-C levels.

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.

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.

Fenofibrate

No case of overdose has been reported with fenofibrate. There is no specific treatment for overdose with fenofibrate. The specific antidote for fenofibrate is not known. Should overdose occur, general supportive care of the patient including monitoring of vital signs and observation of clinical status is indicated. If an overdose is suspected, treat symptomatically and institute appropriate supportive measures as required. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, it cannot be eliminated by hemodialysis.

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.

Fenofibrate

Fenofibrate is a fibric acid derivative whose lipid modifying effects are mediated via activation of peroxisome proliferator activated receptor type alpha (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of atherogenic triglyceride-rich particles (e.g., VLDL) from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity). Activation of PPARα also induces an increase in the synthesis of apoproteins A-I, A-II, and HDL-C. The resulting decrease in TGs produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly.

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.

Fenofibrate

Fenofibrate increases lipolysis of triglyceride (TGs) and VLDL from plasma. Decrease in TGs produces an alteration in the size and composition of LDL. These larger LDL particles are catabolized rapidly. Thus, fenofibrate reduces both, triglycerides as well as cholesterol level from the plasma.

In clinical trials, fenofibrate reduces total cholesterol by 20 to 25%, triglycerides by 40 to 55% and increases HDL-C by 10 to 30%. Because of its significant effect on LDL-C and TGs, treatment with fenofibrate should be beneficial in hypercholesterolemic patients with or without hypertriglyceridaemia.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid. This uricosuric effect of fenofibrate leading to reduction in uric acid levels of approximately 25% should be of additional benefit in those dyslipidemic patients with hyperuricaemia.

Fenofibrate has been shown to possess an anti-aggregatory effect on platelets in animals and in a clinical study, which showed a reduction in platelet aggregation induced by Adenosine diphosphate (ADP), arachidonic acid and epinephrine.

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.

Fenofibrate

Fenofibrate is a pro-drug of the active chemical moiety fenofibric acid. Fenofibrate is converted by ester hydrolysis in the body to fenofibric acid which is the active constituent measurable in the circulation.

Absorption: Fenofibrate is insoluble in water and its bioavailability is optimized when taken with meals. However, after fenofibrate is dissolved, fenofibrate is well absorbed from the gastrointestinal tract. Peak plasma level (C_{max}) of fenofibric acid occurs in around 3 hours after oral administration. The extent of absorption of fenofibrate (AUC) is comparable between fed and fasted conditions. However, food increases the rate of absorption of fenofibrate by approximately 55%. Thus, it is strongly recommended to administer fenofibrate with meals.

Distribution: In healthy volunteers, steady-state plasma levels of fenofibric acid are achieved within a week of dosing. Fenofibric acid is strongly bound to plasma protein (more than 99%). Kinetic studies following the administration of a single dose and continuous treatment of fenofibrate have demonstrated that the drug does not accumulate.

Metabolism: Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid. No unchanged fenofibrate is detected in plasma. Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine. *In vivo* metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Excretion: After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces. Fenofibric acid is eliminated with a half-life of approximately 16 hours. Fenofibric acid is not eliminated by hemodialysis.

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_{0-24h} 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.

Fenofibrate

Carcinogenesis: Two dietary carcinogenicity studies have been conducted in rats with fenofibrate. In the first 24-month study, Wistar rats were dosed with fenofibrate at 10, 45 and 200 mg/kg/day, approximately 0.3, 1, and 6 times the maximum recommended human dose (MRHD), based on body surface area comparisons (mg/m^2). At a dose of 200 mg/kg/day (at 6 times MRHD), the incidence of liver carcinoma was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed in males at 6 times the MRHD.

In a second 24-month study in a different strain of rats (Sprague-Dawley), doses of 10 and 60 mg/kg/day (0.3 and 2 times the MRHD) produced significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in testicular interstitial cell tumors in males at 2 times the MRHD.

In a 21-month study in CF-1 mice, fenofibrate 10, 45 and 200 mg/kg/day (approximately 0.2, 1, and 3 times the MRHD on the basis of mg/m^2 surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18 month study at 10, 60 and 200 mg/kg/day, fenofibrate significantly increased the liver carcinomas in male mice and liver adenomas in female mice at 3 times the MRHD.

Mutagenesis: Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis in primary rat hepatocytes.

Impairment of Fertility: In fertility studies rats were given oral dietary doses of fenofibrate, males received 61 days prior to mating and females 15 days prior to mating through weaning which resulted in no adverse effect on fertility at doses up to 300 mg/kg/day (approximately 10 times the MRHD, based on mg/m^2 surface area comparisons).

7. Description

LIPONORM-F Tablets are White coloured, round, biconvex, one side scored & film coated tablets.

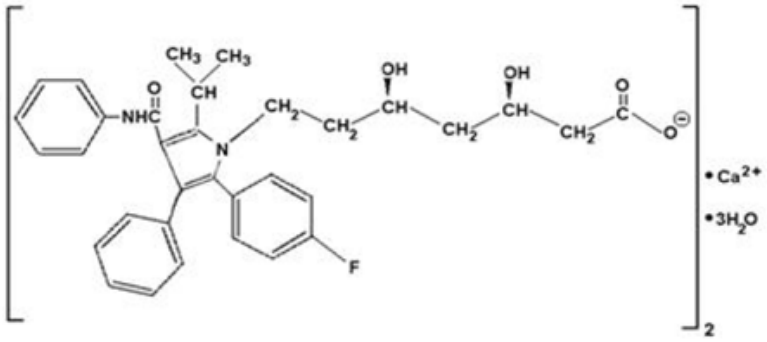
Each tablet of LIPONORM-F contains 10 mg of atorvastatin and 160 mg of fenofibrate (micronized) for oral administration in adults.

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.

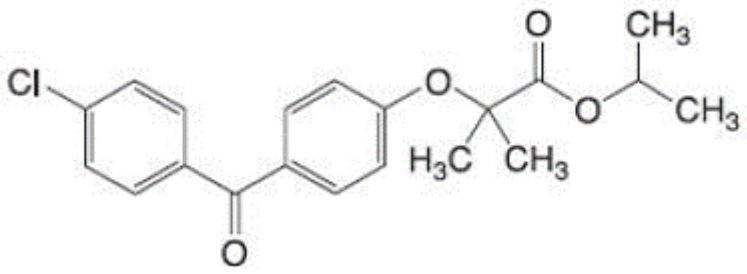
Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water,

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:



Fenofibrate

Fenofibrate is a synthetic phenoxy-isobutyric acid derivate with antihyperlipidemic activity. Fenofibrate is a prodrug which hydrolyzed *in vivo* to its active metabolite fenofibric acid.
Fenofibrate is a white solid crystalline powder which is practically insoluble in water; slightly soluble in methanol, ethanol; soluble in acetone, ether, benzene, chloroform.
Molecular Weight: 360.83 g/mol.
Molecular Formula: C20H21ClO4.
Chemical Name: 2-[4-(4-chlorobenzoyl) phenoxy] 2-methyl-propanoic acid, 1-methylethyl ester.
Structural Formula:



Inactive ingredients (excipients) of LIPONORM-F Tablet contain Microcrystalline Cellulose, Lactose, Starch, Polyvinyl Pyrrolidone K-30, Isopropyl Alcohol, Magnesium Stearate, Talcum, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Hydroxy Propyl Methyl Cellulose, Poly ethylene glycol, Titanium Dioxide & Methylene Chloride.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 Months

8.3Packaging Information

15 tablets per strip.

8.4Storage and Handling Instructions

Store protected from light and moisture, at a temperature not exceeding 30°C.
Keep out of reach of the children.

9. Patient Counseling Information

- Take LIPONORM-F Tablets exactly as prescribed by your doctor. Do not change your dose or stop therapy without talking to your doctor.
- Take LIPONORM-F Tablets once daily at any time of day at about the same time each day. LIPONORM-F Tablets should be taken with food.
- If you miss a dose of LIPONORM-F Tablets, 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 the missed dose.
- Do not take LIPONORM-F Tablets 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-F Tablets if you are breast feeding. This medicine (atorvastatin) can pass into your breast milk and may harm your baby.
- Do not take LIPONORM-F Tablets if you have kidney and/or liver dysfunction.
- LIPONORM-F Tablets 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 this drug therapy. Further, if you have severe side effects such as severe stomach/abdominal pain, persistent nausea/vomiting, yellowing eyes/skin, or dark urine after taking this medicine, contact your doctor.
- 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-F Tablets and certain other medicines can interact with each other causing serious side effects.
- Do not give LIPONORM-F Tablets to other people, even if they have the same problem you have. It may harm them.

10. Details of Manufacturer

Akums Drugs & Pharmaceuticals Ltd.
At : 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. : 4/UA/LL/2014. Date of FDA Product Permission:23/01/2018

12. Date of Revision

May 2021.

Marketed by:

EXCEL BLUE CROSS || EXCEL

Division of

BLUE CROSS LABORATORIES PVT LTD.

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