1.0 NAME OF THE MEDICINAL PRODUCT
MYOTEL-TG
(**Atorvastatin & Fenofibrate Tablets**)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains:
Atorvastatin Calcium USP
eq. to Atorvastatin 10mg
Fenofibrate USP 160mg
Excipients q.s.
Colour: Lake of Quinoline Yellow

3.0 PHARMACEUTICAL FORM:
Film-coated tablet
"Yellow coloured, round, biconvex, film coated tablets".

4.0 CLINICAL PARTICULARS:
4.1 Therapeutic Indications:
Mixed Dyslipidemia
It is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in adult patients with mixed dyslipidemia.

Hyperlipidemia
Myotel-TG is indicated:
- As an adjunct to diet to reduce elevated total-C, LDL-C, ApoB and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial);
- As an adjunct to diet for the treatment of patients with elevated serum TG levels (*Fredrickson* Type IV);
- For the treatment of patients with primary dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet;
- To reduce total-C and LDL-C in patients with HoFH as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable;
- As an adjunct to diet to reduce total-C, LDL-C and ApoB levels in boys and postmenarchal girls, 10 to 17 years of age, with HeFH, if after an adequate trial of diet therapy the following findings are present:

1. LDL-C remains ≥190 mg/dL or
2. LDL-C remains ≥160 mg/dL and:

- there is a positive family history of premature CVD or
- two or more other CVD risk factors are present in the pediatric patient

Severe Hypertriglyceridemia
Myotel-TG is also indicated as adjunctive therapy to diet for treatment of adult patients with severe hypertriglyceridemia. Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually obviate the need for pharmacological intervention.

Markedly elevated levels of serum TG (e.g. >2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of fenofibrate therapy on reducing this risk has not been adequately studied

4.2 Posology and Method of Administration:

Posology

Patients should be placed on an appropriate lipid-lowering diet before receiving ATORLIP-F, and should continue this diet during treatment. The recommended dosage is one tablet once daily

Dosage in Patients with Renal Impairment

Fenofibrate should be initiated at a lower dose in patients having mild to moderately impaired renal function and it should be avoided in patients with severe renal impairment..

Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole or Certain Protease Inhibitors

In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing Myotel-TG and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with Myotel-TG should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of Myotel-TG is employed. In patients taking the HIV protease inhibitor nelfinavir, or the hepatitis C protease inhibitor boceprevir, therapy with Myotel-TG should be limited, and appropriate clinical assessment is recommended.

Method of administration

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

4.3 Contra-Indications:

Myotel-TG is contraindicated in

- Hypersensitivity to either component, atorvastatin or fenofibrate
- Patient with severe renal impairment, including those receiving dialysis
- Patients with active liver disease, including those with primary biliary cirrhosis and unexplained persistent liver function abnormalities
- Patients with preexisting gallbladder disease
- Pregnancy
- Nursing mothers

4.4 Special warnings and Precautions for Use:

Liver Function

The two drugs, given individually, 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 pre-treatment 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 initiating therapy with MYOTEL-TG and repeated as clinically indicated. There have been rare postmarketing 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 MYOTEL-TG, promptly interrupt therapy. If an alternate etiology is not found, do not restart MYOTEL-TG.

MYOTEL-TG 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.
Fenofibrate at doses equivalent to 96 mg to 145 mg per day has been associated with increases in serum transaminases .

In a pooled analysis of 10 placebo-controlled trials, increases to >3 times the ULN occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo. When transaminase determinations were followed, either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appears to be dose-related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least 3 times the ULN was 13% in patients receiving dosages equivalent to 96 mg to 145 mg fenofibrate per day and was 0% in those receiving dosages equivalent to 48 mg or less fenofibrate per day, or placebo.

Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.
Baseline and regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with Atorvastatin & Fenofibrate, and therapy discontinued if enzyme levels persist above 3 times the normal limit.

Skeletal Muscle

The use of Atorvastatin & Fenofibrate may occasionally be associated with myopathy since the two drugs, individually, have been shown to cause myopathy in a small percentage of patients (<1%) in international trials.

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.

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

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 MYOTEL-TG. MYOTEL-TG 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, 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 MYOTEL-TG therapy along with, erythromycin, clarithromycin, a combination of ritonavir plus saquinavir or 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 atorvastatin 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.

Cases of myopathy, including rhabdomyolysis, have been reported with both atorvastatin and fenofibrate co-administered with colchicine, and caution should be exercised when prescribing MYOTEL-TG with colchicine.

Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

Fibrates also increase the risk for myopathy and have been associated with rhabdomyolysis. The risk for serious muscle toxicity appears to be increased in elderly patients and in patients with diabetes, renal insufficiency, or hypothyroidism.

Data from observational studies indicate that the risk for rhabdomyolysis is increased when fibrates, in particular gemfibrozil, are co-administered with an HMG-CoA reductase inhibitor (statin). The combination should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

MYOTEL-TG 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).

Endocrine Function

Increases 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. The effects of 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.

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 vs 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; Hazard Ratio (HR): 1.68, 95% Confidence Interval (CI): 1.09, 2.59; p = 0.0168). The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 vs 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.

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.

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.

Mortality and Coronary Heart Disease Morbidity

The effect of fenofibrate on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

The Action to Control Cardiovascular Risk in Diabetes Lipid (ACCORD Lipid) trial was a randomized placebo-controlled study of 5,518 patients with type 2 diabetes mellitus on background statin therapy treated with fenofibrate. The mean duration of follow-up was 4.7 years. Fenofibrate plus statin combination therapy showed a non-significant 8% relative risk reduction in the primary outcome of major adverse cardiovascular events (MACE), a composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular disease death HR: 0.92, 95% CI: 0.79-1.08) (p=0.32) as compared to statin monotherapy. In a gender subgroup analysis, the hazard ratio for MACE in men receiving combination therapy versus statin monotherapy was 0.82 (95% CI: 0.69-0.99), and the hazard ratio for MACE in women receiving combination therapy versus statin monotherapy was 1.38 (95% CI: 0.98-1.94) (interaction p=0.01). The clinical significance of this subgroup finding is unclear.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a 5-year randomized, placebo-controlled study of 9,795 patients with type 2 diabetes mellitus treated with fenofibrate. Fenofibrate demonstrated a non-significant 11% relative reduction in the primary outcome of coronary heart disease events (HR: 0.89, 95% CI: 0.75-1.05, p=0.16) and

a significant 11% reduction in the secondary outcome of total cardiovascular disease events (HR: 0.89 , p= 0.04). There was a non-significant 11% (HR 1.11 , p=0.18) and 19% (HR 1.19 , p=0.22) increase in total and coronary heart disease mortality, respectively, with fenofibrate as compared to placebo.

Because of chemical, pharmacological, and clinical similarities between fenofibrate, clofibrate and gemfibrozil, the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to fenofibrate.
In the Coronary Drug Project, a large study of post myocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecysitis requiring surgery between the two groups (3.0% vs. 1.8%).

In a study conducted by the World Health Organization (WHO), 5,000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age – adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs 3.96%, p=<0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4,081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% CI for relative risk G:P = 0.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9-year follow-up data from WHO study (RR=1.29).

A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (HR: 2.2, 95% CI: 0.94-5.05). The rate of gallbladder surgery was not statistically significant between study groups, but did trend higher in the gemfibrozil group (1.9% vs 0.3%, p=0.07).

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

Coumarin Anticoagulants
Caution should be exercised when coumarin anticoagulants are given in conjunction with Atorvastatin & Fenofibrate because of the potentiation of coumarin-type anticoagulant

effects in prolonging the PT/INR. To prevent bleeding complications, frequent monitoring of PT/INR and dose adjustment of the anticoagulant are recommended until PT/INR has stabilized.

Pancreatitis
Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil and clofibrate. 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 with obstruction of the common bile duct.

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. Urticaria was seen in 1.1 vs. 0%, and rash in 1.4 vs 0.8% of fenofibrate and placebo patients respectively in controlled trials.

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 blood cell counts are recommended during the first 12 months of Atorvastatin & Fenofibrate administration.

Venothromboembolic Disease
In the FIELD trial, pulmonary embolus (PE) and deep vein thrombosis (DVT) were observed at higher rates in the fenofibrate- than the placebo- treated group. Of 9,795 patients enrolled in FIELD, there were 4,900 in the placebo group and 4,895 in the fenofibrate group. For DVT, there were 48 events (1%) in the placebo group and 67 (1%) in the fenofibrate group ($p= 0.074$); and for PE, there were 32 (0.7%) events in the placebo group and 53 (1%) in the fenofibrate group ($p=0.022$).

In the Coronary Drug Project, a higher proportion of the clofibrate group experienced definite or suspected fatal or non-fatal pulmonary embolism or thrombophlebitis than the placebo group (5.2% vs. 3.3% at five years; $p<0.01$).

Serum Creatinine
Elevations in serum creatinine have been reported in patients on fenofibrate. These elevations tend to return to baseline following discontinuation of fenofibrate. The clinical significance of these observations is unknown. Monitor renal function in patients with renal impairment taking Atorvastatin & Fenofibrate. Renal monitoring should also be considered for patients taking Atorvastatin & Fenofibrate at risk for renal insufficiency such as the elderly and patients with diabetes.

Paradoxical Decreases in HDL Cholesterol Levels
There have been postmarketing and clinical trial reports of severe decreases in HDL cholesterol 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 HDL-C levels be checked within the first few months after initiation of fibrate therapy. If a severely depressed HDL-C level is detected, Atorvastatin & Fenofibrate therapy should be withdrawn, and the HDL-C level monitored until it has returned to baseline, and Atorvastatin & Fenofibrate therapy should not be re-initiated.

4.5 Interaction with other Medicinal Products and Other Forms of Interactions:

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 cytochrome P450 3A4. Concomitant administration of atorvastatin 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 atorvastatin dose exceeds 20 mg.

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor 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.

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.

Moderate CYP3A4 inhibitors: (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin. An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been conducted. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of atorvastatin should be considered and appropriate clinical monitoring of

the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.

Rifampin or Other Inducers of CYP3A4: Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (eg efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of Atorvastatin & Fenofibrate with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

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. The co-administration of Atorvastatin & Fenofibrate with cyclosporine should be avoided.

Gemfibrozil: Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are co-administered with gemfibrozil, concomitant administration of Atorvastatin & Fenofibrate with gemfibrozil should be avoided.

Other Fibrates: 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 & Fenofibrate should be administered with caution when used concomitantly with other fibrates.

Niacin: The risk of skeletal muscle effects may be enhanced when atorvastatin is used in combination with niacin; a reduction in Atorvastatin & Fenofibrate dosage should be considered in this setting.

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 & Fenofibrate. Appropriate clinical monitoring of these patients is recommended.

Colestipol: Plasma concentrations of atorvastatin and its active metabolites were lower (ratio of atorvastatin concentration: 0.74) when colestipol was co-administered with Atorvastatin. However, lipid effects were greater when Atorvastatin and colestipol were co-administered than when either medicinal product was given alone.

Fusidic acid: The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this

interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.
If treatment with systemic fusidic acid is necessary, Atorvastatin & Fenofibrate treatment should be discontinued throughout the duration of the fusidic acid treatment.

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 & Fenofibrate
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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 with atorvastatin and fenofibrate when co-administered with colchicine, and caution should be exercised when prescribing Atorvastatin & Fenofibrate with colchicine.

Coumarin Anticoagulants: Potentiation of coumarin-type anticoagulant effects has been observed with prolongation of the prothrombin time / International Normalized Ratio (PT/INR). Caution should be exercised when coumarin anticoagulants are given in conjunction with Atorvastatin & Fenofibrate. The dosage of the anticoagulants 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.

Immunosuppressants: Immunosuppressants such as cyclosporine and tacrolimus can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including fenofibrate, there is a risk that an interaction will lead to deterioration or renal function. The benefits and risks of using Atorvastatin & Fenofibrate with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed and renal function monitored.

Bile Acid Resins: Since bile acid sequestrants may bind other drugs given concurrently, patients should take Atorvastatin & Fenofibrate at least 1 hour before or 4 to 6 hours after a bile acid-binding resin to avoid impeding fenofibrate absorption.

Glitazones: Some cases of reversible paradoxical reduction of HDL-C have been reported during concomitant administration of fenofibrate and glitazones. Therefore it is recommended to monitor HDL-C if Atorvastatin & Fenofibrate is co-administered with a glitazone and stopping either therapy if HDL-C is too low.

Renal Impairment

Fenofibrate should be initiated at a lower dose in patients having mild to moderately impaired renal function and it should be avoided in patients with severe renal impairment.

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Hepatic Impairment

Atorvastatin is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels. The use of fenofibrate has not been evaluated in subjects with hepatic impairment. Thus, Atorvastatin & Fenofibrate cannot be used in patients with active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels.

4.6 Pregnancy and lactation:

Pregnancy

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 as well as fenofibrate use during pregnancy. There have been rare reports of congenital anomalies following intrauterine exposure to statins.

Safety of fenofibrate in pregnant women has not been established. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

MYOTEL-TG 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 MYOTEL-TG , 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.

Lactation

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. Because another drug in class of statin 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. Fenofibrate should not be used in nursing mothers.
MYOTEL-TG should not be used in nursing mothers.

Pediatric Use

Safety and efficacy of both atorvastatin and fenofibrate in pediatric patients have not been established.

Geriatric Use

No overall differences in safety or effectiveness of atorvastatin were observed between elderly 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.

Fenofibric acid is known to be substantially excreted by the kidneys, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Fenofibric acid exposure is not influenced by age. Since, elderly patients have a higher incidence of renal impairment; dose selection for the elderly should be made on the basis of renal function. Elderly patients with normal renal function should require no dose modifications. Consider monitoring renal function in elderly patients taking fenofibrate

4.7 Effects on ability to drive and use machine:
Atorvastatin has negligible influence on the ability to drive and use machines.

4.8 Undesirable Effects:
The common side effects are Inflammation of the nasal passages, hair loss, itching, pain in the throat, nose bleed, Allergic reactions, Increases in blood sugar levels (if you have diabetes continue careful monitoring of your blood sugar levels), increase in blood creatine kinase, Headache Nausea, constipation, wind, indigestion, diarrhea, Joint pain, muscle pain and back pain and Blood test results that show your liver function can become abnormal (mild change in liver enzyme)

Other adverse reactions reported include:

- *Body as a Whole:* malaise, pyrexia
- *Musculoskeletal and Connective Tissue Disorders:* myalgia, arthralgia, pain in extremity, muscle spasms, muscle fatigue, back pain, neck pain, joint swelling, myopathy, myositis, rhabdomyolysis, tendonopathy, sometimes complicated by rupture
- *Metabolic and Nutritional System:* transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, CPK increase, hyperglycemia, hypoglycemia, weight gain, anorexia
- *Nervous System:* headache, dizziness, paresthesia, hypesthesia, dysgeusia, amnesia, peripheral neuropathy, nightmare, insomnia
- *Respiratory*, *Thoracic and Mediastinal Disorders:* epistaxis, nasopharyngitis, pharyngolaryngeal pain
- *Skin and Appendages:* urticaria, skin rash, pruritus, alopecia, angioneurotic edema, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis
- *Urogenital System:* white blood cells, urine positive
- *Blood and Lymphatic System Disorders:* thrombocytopenia
- *Immune System Disorders:* allergic reactions, anaphylaxis
- *Eye Disorders:* vision blurred, visual disturbance
- *Ear and Labyrinth Disorders:* tinnitus, hearing loss
- *Gastrointestinal Disorders:* constipation, flatulence, dyspepsia, nausea, diarrhea, vomiting, abdominal pain upper and lower, eructation, pancreatitis

- *Hepatobiliary Disorders:* hepatitis, cholestasis, hepatic failure
- *Reproductive System and Breast Disorders:* gynecomastia

4.9 Overdoses:

There is no specific treatment available for Atorvastatin & Fenofibrate overdosage. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Due to extensive drug binding to plasma proteins, hemodialysis should not be considered.

5.0 PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Atorvastatin

Atorvastatin is a selective, competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme that converts 3-HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. Atorvastatin reduces low density lipoprotein (LDL) production and the number of LDL particles. Triglycerides (TG) and cholesterol in the liver are incorporated into very low density lipoprotein (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 high density lipoprotein-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 (HoFH), a population that rarely responds to other lipid-lowering medication(s).

Atorvastatin has been shown to reduce concentrations of total-C (30%-46%), LDL-C (41%-61%), ApoB (34%-50%), and TG (14%-33%) while producing variable increases in HDL-C and ApoA1 in a dose response study. These results are consistent in patients with heterozygous familial hypercholesterolemia (HeFH), nonfamilial forms of hypercholesterolemia, and mixed hyperlipidemia, including patients with noninsulin-dependent diabetes mellitus. Reductions in total-C, LDL-C, and ApoB have been proven to reduce risk for cardiovascular events and cardiovascular mortality.

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.

Fenofibrate
The pharmacological effects of fenofibric acid in both animals and humans have been extensively studied through oral administration of fenofibrate.

The lipid-modifying effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor alpha (PPAR-alpha). Through this mechanism, fenofibrate increases lipolysis and elimination of TG-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity).

The resulting decrease in TG 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. Activation of PPAR-alpha also induces an increase in the synthesis of apo AI, AII and HDL-C.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B, an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of HDL-C and its transport complex, apolipoprotein A (apo AI and apo AII) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and TG and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering TG on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL-C, apo B, total TG and TG-rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in HDL-C and apo AI and apo AII. The overall effect is a decrease in the ratio of LDL and VLDL to HDL.

5.2 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 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 C_{max} and area under the 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.

Plasma concentrations of fenofibric acid after administration of one 145 mg tablets are equivalent under fed conditions to one 200 mg micronized fenofibrate capsule. Fenofibrate is a pro-drug of the active chemical moiety fenofibric acid. Fenofibrate is converted by ester hydrolysis in the body of fenofibric acid which is the active constituent measurable in the circulation. The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabeled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration. Exposure to fenofibric acid in plasma, as measured by C_{max} and AUC, is not significantly different when a single 145 mg dose of fenofibrate is administered under fasting or nonfasting conditions.

Distribution
Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/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.

Upon multiple dosing of fenofibrate, fenofibric acid steady state is achieved within 9 days. Plasma concentrations of fenofibric acid at steady state are approximately double of those following a single dose. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

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. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome (CYP) P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

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

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.

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabeled 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 20 hours, allowing once daily dosing.

Special Population
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.

In elderly volunteers 77 to 87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly with normal renal function, without increasing accumulation of the drug or metabolites.

Pediatric: Apparent oral clearance of atorvastatin in pediatric subjects appeared similar to that of adults when scaled allometrically by body weight as the body weight was the only significant covariate in atorvastatin population pharmacokinetics (PK) model with data including pediatric HeFH patients (ages 10 years to 17 years of age, n=29) in an open-label, 8-week study.

The pharmacokinetics of fenofibrate has not been studied in pediatric populations.
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. No pharmacokinetic difference between males and females has been observed for fenofibrate.

Renal Impairment: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, atorvastatin dose adjustment in patients with renal dysfunction is not necessary.

The pharmacokinetics of fenofibric acid was examined in patients with mild, moderate, and severe renal impairment. Patients with severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73m^2) showed 2.7-fold increase in exposure for fenofibric acid and increased accumulation of fenofibric acid during chronic dosing compared to that of healthy subjects. Patients with mild to moderate renal impairment (eGFR 30-59 mL/min/1.73m^2) had similar exposure but an increase in the half-life for fenofibric acid compared to that of healthy subjects. Based on these findings, the use of Atorvastatin &

Fenofibrate should be avoided in patients who have severe renal impairment and dose reduction is required in patients having mild to moderate renal impairment.

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 Childs-Pugh A disease. C_{max} and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease. No pharmacokinetic studies for fenofibrate have been conducted for fenofibrate in patients having hepatic impairment.

Race: The influence of race on the pharmacokinetics of fenofibrate has not been studied; however fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability

5.3 Pre-clinical safety data:

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 fold the AUC0-24h 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 fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses fetal 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. It is not known whether atorvastatin or its metabolites are excreted in human milk

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. 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 (~10 times the MRHD, based on mg/m2 surface area comparisons).

6.0 PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients:

Tablet Core:
Lactose Monohydrate
Colloidal Anhydrous Silica

Maize Starch
Sodium Starch Glycolate (Type A)
Magnesium Stearate
Purified Talc
Croscarmellose Sodium
Tablet Coat
Hypromellose (Hydroxy Propyl Methyl Cellulose)
Purified Talc
Macrogols (PEG-6000)
Titanium Dioxide
Lake of Quinoline Yellow

6.2 Incompatibilities:
Not known - It is a well-developed established product. No incompatibility data is available.

6.3 Shelf-life:
24 months from the month of manufacturing.

6.4 Special Precautions for Storage:
Store below 30°C, in well closed container. Protect from light

6.5 Nature and Contents of Container:
1x10 Tablets in Alu- Alu blister in a carton

7 MARKETING AUTHORIZATION HOLDER:
UNIMAX LABORATORIES
Plot No.7, Sector 24,
Faridabad-121005, Haryana, India

8 MARKETING AUTHORIZATION NUMBER:
Fresh Registration

9 DATE OF FIRST AUTHORIZATION/RENEWALOF AUTHORIZATION:
Fresh Registration

10. DATE OF REVISION OF TEXT:
Not Applicable