FENOLIP 145 Tablets (Fenofibrate)

**Composition**

**FENOLIP-145**
Each tablet contains:
Fenofibrate ..............145 mg

**Dosage Form**
Tablet

**Pharmacology**

**Pharmacodynamics**

The active moiety of FENOLIP is fenofibric acid. 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 triglyceride (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 low-density lipoprotein (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 apolipoproteins A-I, A-II and high-density lipoprotein cholesterol (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 cholesterol (total-C), LDL cholesterol (LDL-C), and apolipoprotein B (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-C, LDL-C, apo B,
total TG and TG-rich lipoprotein [very low density lipoprotein (VLDL)] in treated patients. In addition, treatment with fenofibrate results in increases in HDL-C, apo AI and apo AII. The overall effect is a decrease in the ratio of LDL and VLDL to HDL.

**Pharmacokinetics**

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 to fenofibric acid, which is the active constituent measurable in the circulation.

**Absorption**

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 maximum plasma concentration ($C_{\text{max}}$) and area under curve (AUC), is not significantly different when a single 145 mg dose of fenofibrate is administered under fasting or nonfasting conditions.

**Distribution**

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**

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 the 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 [CYP] 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 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 Populations**
**Geriatric:** 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:** The pharmacokinetics of fenofibrate has not been studied in pediatric populations.

**Gender:** No pharmacokinetic difference between males and females has been observed for fenofibrate.

**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.

**Renal Impairment:** 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 [eGFR] <30 mL/min/1.73 m$^2$) 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/1.73 m$^2$) 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 FENOLIP should be avoided in patients who have severe renal impairment and dose reduction is required in patients having mild-to-moderate renal impairment.

**Hepatic Impairment:** No pharmacokinetic studies have been conducted in patients with hepatic impairment.

**Indications**

**Primary Hypercholesterolemia or Mixed Dyslipidemia**

FENOLIP is indicated as adjunctive therapy to diet to reduce elevated LDL-C, total-C, TG and apo B and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia.

**Severe Hypertriglyceridemia**

FENOLIP 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.

**Important Limitations of Use**

Fenofibrate at a dose equivalent to 145 mg of FENOLIP was not shown to reduce coronary heart disease morbidity and mortality in a large, randomized controlled trial of patients with type 2 diabetes mellitus.

**Dosage and Administration**
General Considerations

Patients should be placed on an appropriate lipid-lowering diet before receiving FENOLIP, and should continue this diet during treatment with FENOLIP. FENOLIP tablets can be given without regard to meals.

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in the hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, thiazide diuretics and beta-blockers are sometimes associated with massive rises in plasma TG, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of FENOLIP if lipid levels fall significantly below the targeted range.

Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 145 mg once daily.

Primary Hypercholesterolemia or Mixed Dyslipidemia

The initial dose of FENOLIP is 145 mg once daily.

Severe Hypertriglyceridemia

The initial dose is 145 mg per day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4- to 8-week intervals. The maximum dose is 145 mg once daily.

Renal Impairment

Treatment with FENOLIP should be initiated at a dose of 48 mg per day in patients having mild-tomoderately impaired renal function and increased only after evaluation of the effects on renal function and lipid levels at this dose. The use of FENOLIP should be avoided in patients with severe renal impairment.

Geriatric Patients

Dose selection for the elderly should be made on the basis of renal function.

Contraindications

FENOLIP is contraindicated in:

- 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 pre-existing gallbladder disease
- Patients with known hypersensitivity to fenofibrate or fenofibric acid
- Pregnancy and lactation
Warnings and Precautions

Drug Interactions

**Coumarin Anticoagulants:** Potentiation of coumarin-type anticoagulant effects has been observed with prolongation of the prothrombin time or international normalized ratio (PT/INR). Caution should be exercised when coumarin anticoagulants are given in conjunction with FENOLIP. 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 of renal function. The benefits and risks of using FENOLIP with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed and renal function monitored.

**Bile Acid-binding Resins:** Since bile acid-binding resins may bind other drugs given concurrently, patients should take FENOLIP 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 with fenofibrate co-administered with colchicine, and caution should be exercised when prescribing FENOLIP with colchicine.

**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 FENOLIP is co-administered with a glitazone and stopping either therapy if HDL-C is too low.

*In vitro* studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of CYP P450 isoforms; CYP3A4, CYP2D6, CYP2E1 or CYP1A2. They are weak inhibitors of CYP2C8, CYP2C19 and CYP2A6 and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Table 1 describes the effects of co-administered drugs on fenofibric acid systemic exposure and Table 2 describes the effects of co-administered fenofibrate or fenofibric acid on other drugs.

**Table 1: Effects of co-administered drugs on fenofibric acid systemic exposure from fenofibrate administration**

<table>
<thead>
<tr>
<th>Co-Administered Drug</th>
<th>Dosage Regimen of Co-administered Drug</th>
<th>Dosage Regimen of Fenofibrate*</th>
<th>Changes in Fenofibric Acid Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AUC C&lt;sub&gt;max&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Lipid-lowering agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>20 mg once daily for 10 days</td>
<td>Fenofibrate 160 mg&lt;sup&gt;1&lt;/sup&gt; once daily for 10 days</td>
<td>2% 4%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40 mg as a single dose</td>
<td>Fenofibrate 3 x 67 mg&lt;sup&gt;2&lt;/sup&gt; as a single dose</td>
<td>1% 2%</td>
</tr>
</tbody>
</table>
Fluvastatin | 40 mg as a single dose | Fenofibrate 160 mg\(^1\) as a single dose | 2% | 10%

**Anti-diabetic agents**

| Glimepiride | 1 mg as a single dose | Fenofibrate 145 mg\(^1\) once daily for 10 days | 1% | 1%
| Metformin | 850 mg three times daily for 10 days | Fenofibrate 54 mg\(^1\) three times daily for 10 days | 9% | 6%
| Rosiglitazone | 8 mg once daily for 5 days | Fenofibrate 145 mg\(^1\) once daily for 14 days | 10% | 3%

* Plasma concentrations of fenofibric acid after administration of one 145 mg tablet are equivalent under fed conditions to one 200 mg capsule.

\(^1\)Fenofibrate oral tablet

\(^2\)Fenofibrate oral micronized capsule

Table 2: Effects of fenofibrate co-administration on systemic exposure of other drugs

<table>
<thead>
<tr>
<th>Dosage Regimen of Fenofibrate</th>
<th>Dosage Regimen of Co-Administered Drug</th>
<th>Change in Co-Administered Drug Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed lipid-lowering agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenofibrate 160 mg(^1) once daily for 10 days</td>
<td>Atorvastatin, 20 mg once daily for 10 days</td>
<td>Atorvastatin 17% 0%</td>
</tr>
<tr>
<td>Fenofibrate 3 × 67 mg(^2) as a single dose</td>
<td>Pravastatin, 40 mg as a single dose</td>
<td>Pravastatin 13% 13%</td>
</tr>
<tr>
<td>Fenofibrate 160 mg(^1) as a single dose</td>
<td>Fluvastatin, 40 mg as a single dose</td>
<td>(+)-3R, 5S-Fluvastatin 26% 29%</td>
</tr>
</tbody>
</table>

**Anti-diabetic agents**

| Fenofibrate 145 mg\(^1\) once daily for 10 days | Glimepiride, 1 mg as a single dose | Glimepiride 35% 18% |
| Fenofibrate 54 mg\(^1\) three times daily for 10 days | Metformin, 850 mg three times daily for 10 days | Metformin 3% 6% |
| Fenofibrate 145 mg\(^1\) once daily for 14 days | Rosiglitazone, 8 mg once daily for 5 days | Rosiglitazone 6% 1% |

\(^1\)Fenofibrate oral tablet

\(^2\)Fenofibrate oral micronized capsule

**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 5518 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 (hazard ratio [HR]: 0.92, 95% CI: 0.79-1.08) (p=0.32) as compared to statin monotherapy. In a gender subgroup analysis, the HR for MACE in men receiving combination therapy vs. statin monotherapy was 0.82 (95% CI: 0.69-0.99), and the HR for MACE in women receiving combination therapy vs. 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 [0.80-0.99], p=0.04). There was a non-significant 11% (HR: 1.11 [0.95, 1.29], p=0.18) and 19% (HR: 1.19 [0.90, 1.57], 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 four 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 cholecystitis 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 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 3.5-year 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 the 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).

**Skeletal Muscle**

Fibrates 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.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase (CPK) levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and **FENOLIP** therapy should be discontinued if markedly elevated CPK levels occur or myopathy/myositis is suspected or diagnosed.

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.

Cases of myopathy, including rhabdomyolysis, have been reported with fenofibrate co-administered with colchicine, and caution should be exercised when prescribing **FENOLIP** with colchicine.

**Liver Function**

Fenofibrate at doses equivalent to 96 mg to 145 mg per day has been associated with increases in serum transaminases [aspartate transaminase (AST)/serum glutamic oxaloacetic transaminase (SGOT) or alanine transaminase (ALT)/serum glutamic pyruvic transaminase (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to >3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate vs. 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 appear to be dose-related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least 3 times the upper limit of normal 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 **FENOLIP**, and therapy discontinued if enzyme levels persist above three times the normal limit.

**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 **FENOLIP**. Renal monitoring should also be considered for patients taking **FENOLIP** at risk for renal insufficiency such as the elderly and patients with diabetes.

**Cholelithiasis**

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

**Coumarin Anticoagulants**

Caution should be exercised when coumarin anticoagulants are given in conjunction with FENOLIP 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.

**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 blood cell counts is recommended during the first 12 months of FENOLIP administration.

**Hypersensitivity Reactions**

*Acute Hypersensitivity*

Anaphylaxis and angioedema have been reported postmarketing with fenofibrate. In some cases, reactions were life-threatening and required emergency treatment. If a patient develops signs or symptoms of an acute hypersensitivity reaction, advise them to seek immediate medical attention and discontinue fenofibrate.

*Delayed Hypersensitivity*

Severe cutaneous adverse drug reactions (SCAR), including Stevens-Johnson syndrome, toxic epidermal necrolysis, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have been reported postmarketing, occurring days to weeks after initiation of fenofibrate. The cases of DRESS were associated with cutaneous reactions (such as rash or exfoliative dermatitis) and a combination of eosinophilia, fever, systemic organ involvement (renal, hepatic, or respiratory). Discontinue fenofibrate and treat patients appropriately if SCAR is suspected.

**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 thrombophysletitis than the placebo group (5.2%
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 apo 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, fibrate therapy should be withdrawn, and the HDL-C level monitored until it has returned to baseline, and fibrate therapy should not be re-initiated.

Interstitial Lung Disease

Cases of interstitial lung disease have been reported with fenofibrate, especially with long term therapy. Presenting features can include dyspnea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, FENOLIP therapy should be discontinued.

Diabetes Mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30 kg/m$^2$, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Renal Impairment

The use of FENOLIP should be avoided in patients who have severe renal impairment. Dose reduction is required in patients with mild-to-moderate renal impairment. Monitoring renal function in patients with renal impairment is recommended.

Hepatic Impairment

The use of fenofibrate has not been evaluated in subjects with hepatic impairment.

Pregnancy

Safety in pregnant women has not been established. There are no adequate and well controlled studies of fenofibrate in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant rats given oral dietary doses of 14, 127, and 361 mg/kg/day from gestation day 6-15 during the period of organogenesis, adverse developmental findings were not observed at 14 mg/kg/day (less than 1 times the MRHD, based on body surface area comparisons; mg/m$^2$). Increased fetal skeletal malformations were observed at maternally toxic doses (361 mg/kg/day, corresponding to 12 times the clinical exposure at the MRHD) that significantly suppressed maternal
body weight gain. In pregnant rabbits given oral gavage doses of 15, 150 and 300mg/kg/day from gestation day 6-18 during the period of organogenesis and allowed to deliver, aborted litters were observed at 150mg/kg/day (≥10 times the MRHD, based on body surface area comparisons: mg/m²). No adverse developmental findings were observed at 15mg/kg/day (at less than 1 times the MRHD, based on body surface area comparisons; mg/m²).

In pregnant rats given oral dietary doses of 15, 75, and 300 mg/kg/day from gestation day 15 through lactation day 21 (weaning), maternal toxicity was observed at less than 1 times the MRHD, based on body surface area comparisons; mg/m². Post-implantation loss was observed at ≥ 75 mg/kg/day (≥ 2 times the clinical exposure at the MRHD) in the presence of maternal toxicity (decreased weight gain). Decreased pup survival was noted at 300 mg/kg/day (10 times the clinical exposure at the MRHD), which was associated with decreased maternal body weight gain/maternal neglect.

**Lactation**

There is no available information on the presence of fenofibrate in human milk, effects of the drug on the breastfed infant, or the effects on milk production. Fenofibrate is present in the milk of rats, and is therefore likely to be present in human milk. Because of the potential for serious adverse reactions in breastfed infants, such as disruption of infant lipid metabolism, women should not breastfeed during treatment with fenofibrate and for 5 days after the final dose.

**Pediatric Use**

Safety and efficacy have not been established in pediatric patients.

**Geriatric Use**

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 FENOLIP.

**Undesirable Effects**

**Clinical Trials Experience**

Because clinical studies are conducted under widely varying conditions, adverse reactions 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 the rates observed in practice.

Adverse events reported by 2% or more of patients treated with fenofibrate (and greater than placebo) during the double blind, placebo-controlled trials, regardless of causality, are listed in the Table 3 below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

**Table 3: Adverse reactions reported by 2% or more of patients treated with fenofibrate and greater than placebo during the double-blind, placebo-controlled trials**
<table>
<thead>
<tr>
<th>BODY SYSTEM</th>
<th>Fenofibrate* (N= 439)</th>
<th>Placebo (N=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abdominal Pain</strong></td>
<td>4.6%</td>
<td>4.4%</td>
</tr>
<tr>
<td><strong>Back Pain</strong></td>
<td>3.4%</td>
<td>2.5%</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>3.2%</td>
<td>2.7%</td>
</tr>
<tr>
<td><strong>DIGESTIVE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2.3%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.1%</td>
<td>1.4%</td>
</tr>
<tr>
<td><strong>METABOLIC AND NUTRITIONAL DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal Liver Function Tests</td>
<td>7.5%**</td>
<td>1.4%</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>3.0%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Increased CPK</td>
<td>3.0%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Increased AST</td>
<td>3.4%**</td>
<td>0.5%</td>
</tr>
<tr>
<td><strong>RESPIRATORY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Disorder</td>
<td>6.2%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2.3%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

* Dosage equivalent to 145 mg fenofibrate

** Significantly different from placebo

**Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of fenofibrate: myalgia, rhabdomyolysis, pancreatitis, acute renal failure, muscle spasm, hepatitis, cirrhosis, anemia, arthralgia, decreases in hemoglobin, decreases in hematocrit, white blood cell decreases, asthenia and severely depressed 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.

Additional adverse reactions observed in clinical trials and postmarketing experience include:

- **Immune system disorders**: hypersensitivity
- **Vascular disorders**: thromboembolism (pulmonary embolism, deep vein thrombosis)
- **Hepatobiliary disorders**: cholelithiasis, complications of cholelithiasis (e.g. cholecystitis, cholangitis, biliary colic etc.)
- **Skin and subcutaneous tissue disorders**: severe cutaneous reactions (e.g. erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, etc.), cutaneous hypersensitivity (e.g. rash, pruritus, urticaria), alopecia, photosensitivity reactions
- **Reproductive system and breast disorders**: sexual dysfunction
- **Investigations**: blood homocysteine level increased, blood urea increased

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 18002677779 (Cipla Number) or you can report to PvPI on 1800 180
By reporting side-effects, you can help provide more information on the safety of this product.

**Overdosage**

There is no specific treatment for overdose with FENOLIP. 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. Because fenofibric acid is highly bound to plasma proteins, hemodialysis should not be considered.

**Incompatibility**

None

**Shelf-Life**

2 years

**Storage and Handling Instructions**

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

**Packaging**

**FENOLIP-145:** Blister pack of 10 tablets

**Last Updated:** November 2018

**Last Reviewed:** November 2018