5.1 Mortality and Coronary Heart Disease Morbidity

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were randomized to fenofibrate, placebo, or aspirin; the combined endpoint of non-fatal myocardial infarction, non-fatal stroke, and coronary death was lower in the fenofibrate group than in the placebo group (9.9% vs. 11.3%, p=0.047). However, no difference was observed between the fenofibrate and placebo groups for fatal coronary events. The combined endpoint of non-fatal myocardial infarction, non-fatal stroke, and coronary death was lower in the aspirin group than in the placebo group (9.9% vs. 11.3%, p=0.047). However, no difference was observed between the aspirin and placebo groups for fatal coronary events. The combined endpoint of non-fatal myocardial infarction, non-fatal stroke, and coronary death was lower in the fenofibrate group than in the placebo group (9.9% vs. 11.3%, p=0.047). However, no difference was observed between the fenofibrate and placebo groups for fatal coronary events.

5.2 Skeletal Muscle

Serious myalgia has been reported, including myoglobinuria, and has been reported with and without myoglobinuria. The risk for serious muscle toxicity appears to be higher in elderly patients and in patients with diabetes, renal impairment, or hypothyroidism. The use of FENOGLIDE should be avoided in patients with severe renal impairment (creatinine clearance < 30 mL/min).

5.3 Liver Function

Fenofibrate increases cholesterol excretion into the bile, leading to risk of cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. (5.5)

5.5 Geriatric Use

Baseline and regular periodic monitoring of liver tests, including ALT (SGOT) and ALP (SGPT), should be performed for the first 12 months of treatment with FENOGLIDE and therapy discontinuation if enzyme levels peak twice above the normal level.

8.1 Pregnancy

Fenofibrate should not be used in nursing mothers. A decision should be made whether to discontinue the drug or discontinue breastfeeding based on the importance of the drug to the mother.

8.2 Postmarketing Experience

The following adverse reactions have been identified postmarketing in fenofibrate use. Because many of these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency. The reported reactions are listed under the following headings: cutaneous adverse reactions, gastrointestinal adverse reactions, hepatic adverse reactions, musculoskeletal adverse reactions, and other adverse reactions. These adverse reactions are classified according to body system and are listed in order of decreasing frequency. Adverse reactions reported by 2% or more of patients treated with fenofibrate and greater than placebo are shown in the following table. Adverse reactions reported by 1% of patients treated with fenofibrate are shown in the following table.

8.3 Other Adverse Reactions

Fenofibrate should not be used in patients with pre-existing gallbladder disease or who are at high risk of developing gallbladder disease. In an 18-month, double-blind, placebo-controlled clinical trial in patients with high triglyceridemia, fenofibrate caused a five-fold increase in the risk of gallbladder disease. In a study of 11,500 patients treated with fenofibrate or placebo, gallstone incidence was 3.2% in the fenofibrate group and 1.4% in the placebo group. The incidence of gallstones was 5.3% in patients taking fenofibrate versus 1.1% of patients treated with placebo. When fenofibrate is taken with other drugs known to be associated with cholelithiasis, including bile acid binding resins, gallbladder disease should be anticipated. If gallstones are found, fenofibrate should be discontinued.

8.4 Nitrofurantoin

Nitrofurantoin should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min).

8.5 Geriatric Use

The efficacy and safety of fenofibrate in elderly patients have been adequately assessed in controlled trials. The clinical relevance of this information to elderly patients is unknown, and the results of studies do not necessarily predict the behavior in an elderly population. The dosage of fenofibrate should be reduced in patients over the age of 65 years, and the dosage should be increased in patients with impaired renal function.

8.6 Pregnancy

Fenofibrate should not be used in pregnancy. There are no adequate and well-controlled studies in pregnant women. Fenofibrate has been shown to cause delayed skeletal and organ development in rats and rabbits. The use of fenofibrate in pregnant women may cause fetal harm and should be avoided. Fenofibrate is teratogenic when administered during organogenesis in both rats and rabbits. In rats, administration of fenofibrate to pregnant animals at doses equivalent to 87 mg to 130 mg fenofibrate per day (at the highest dose, comparable to a human dose of 150 mg/day) caused an increased rate of fetal resorption, delayed ossification, and skeletal variations. In rabbits, administration of fenofibrate at doses equivalent to 87 mg to 130 mg fenofibrate per day (at the highest dose, comparable to a human dose of 150 mg/day) caused a delay in ossification of the ribs and sternebrae. Therefore, fenofibrate should be avoided in pregnant women.

8.7 Hepatic Impairment

The following adverse reactions have been identified postmarketing in patients with severe hepatic impairment: cholestatic jaundice (0.1%), hepatitis (0.1%), and elevated liver enzymes (0.1%). In patients with severe hepatic impairment, fenofibrate should be avoided. In patients with mild hepatic impairment, fenofibrate should be used with caution. In patients with moderate hepatic impairment, fenofibrate should be used with great caution.

8.8 Transaminase Elevations

Fenofibrate can increase serum transaminases. Monitor liver tests, including ALT, periodically during treatment. If transaminase levels rise to twice the upper limit of normal or greater and if associated with clinical symptoms of hepatic injury, discontinue fenofibrate.

8.9 Warfarin

Fenofibrate increases the risk of bleeding in patients taking oral anticoagulants. Concomitant use should be avoided if possible. If concurrent use is necessary, warfarin and/or oral anticoagulants should be titrated to maintain the INR between 2 and 3. Monitor INR periodically.

9.2 Drug Interactions

Fenofibrate should be administered at a dose of 140 mg per day to patients with mild renal impairment.

9.3 Contraindications

Fenofibrate should be administered at a dose of 140 mg per day to patients with mild renal impairment.
The melting point is 79° to 82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

12.3 Pharmacokinetics

Fenofibrate results in increases in HDL and apoproteins apo AI and apo AII. A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B, an LDL atherogenic due to their susceptibility to oxidation, to large buoyant particles. These larger particles have an alteration in the size and composition of LDL from small, dense particles (which are thought to be of atherogenic nature) to large buoyant particles.

Fenofibrate also reduces serum apo B and VLDL-C in hypertriglyceridemia and non-hypertriglyceridemic individuals by increasing a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPAR also induces hepatic triglyceride lipase activity.

The pharmacokinetics of fenofibric acid were examined in patients with mild, moderate, and severe renal impairment. There was no specific treatment for overdose with FENOGLIDE. General supportive care of the patient is required in patients having mild to moderate renal impairment and dialysis is required in patients having severe renal impairment (Creatinine clearance [CrCl] ≤30 mL/min or estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m2).

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259	Four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the... some with baseline TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia... times daily for 10 days (Study 1). Placebo (n=116) -3.0% -6.6% +2.3% +0.9% FENOGLIDE® (fenofibrate) Tablets 40 mg, are white to off-white oval tablets debossed "FLO" on one side and "40" on the other side.

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Baseline TG levels

28 449 450 -0.5 27 432 223 -46.2*

Total Cholesterol 44 272 271 0.4 48 261 223 -13.8*

VLDL Cholesterol 42 137 142 11.0 45 126 54 -49.4*

HDL Cholesterol 79 47 57 11.1 81 51 36 -30.8*}


tablet

FENOGLIDE® (fenofibrate) Tablets 40 mg, are white to off-white oval tablets debossed "FLO" on one side and "40" on the other side.

Table 4. Mean Percent Change in Lipid Parameters at End of Treatment

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Baseline LDL-C</th>
<th>Baseline HDL-C</th>
<th>Baseline TG</th>
<th>FENOGLIDE 40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in LDL-C (%)</td>
<td>-14% 17%</td>
<td>15% 6%</td>
<td>16% 0%</td>
<td></td>
</tr>
<tr>
<td>Change in HDL-C (%)</td>
<td>+13% -10%</td>
<td>+15% -8%</td>
<td>+12% -3%</td>
<td></td>
</tr>
<tr>
<td>Change in TG (%)</td>
<td>+17% 0%</td>
<td>+15% -6%</td>
<td>+16% 0%</td>
<td></td>
</tr>
</tbody>
</table>

In a subset of the subjects, measurements of apo B were conducted. Fenofibrate treatment significantly reduced total-C by 15% from baseline to concomitant with comparable with placebo (p<0.05 vs. 4-6% in Study 1).

The pharmacokinetics of fenofibric acid were examined in patients with mild, moderate, and severe renal impairment. There was no specific treatment for overdose with FENOGLIDE. General supportive care of the patient is required in patients having mild to moderate renal impairment and dialysis is required in patients having severe renal impairment (Creatinine clearance [CrCl] ≤30 mL/min or estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m2).