Therapeutic Class Overview
Fibric Acid Derivatives

Therapeutic Class

- **Overview/Summary:** The fibric acid derivatives are agonists of the peroxisome proliferator activated receptor α (PPARα). Activation of PPARα increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII. The resulting decrease in triglycerides (TG) produces an alteration in the size and composition of low-density lipoprotein cholesterol (LDL-C) from small, dense particles to large buoyant particles. There is also an increase in the synthesis of high-density lipoprotein cholesterol (HDL-C), as well as apoprotein AI and AII.[1-10] The major action of this class of medications is to reduce TG. The fibric acid derivatives can decrease TG by 20 to 50% and increase HDL-C by 10 to 35%. They also lower LDL-C by 5 to 20%; however, in patients with hypertriglyceridemia, LDL-C may increase with the use of fibric acid derivatives.[11]

  Several fenofibrate products are currently available, including micronized and non-micronized formulations. The different fenofibrate formulations are not equivalent on a milligram-to-milligram basis. Micronized fenofibrate is more readily absorbed than non-micronized formulations, which allows for a lower daily dose. Fenofibrate (micronized and non-micronized formulations), fenofibric acid, and gemfibrozil are available generically in at least one dosage form and/or strength.[12] Fenofibrate and fenofibric acid are Food and Drug Administration (FDA)-approved for the adjunctive treatment of primary hypercholesterolemia or mixed dyslipidemias, as well as an adjunctive treatment for hypertriglyceridemia. Gemfibrozil is FDA-approved for the treatment of hypertriglyceridemia and to reduce the risk of developing coronary heart disease (CHD) in select patients.[13] Gemfibrozil has demonstrated a reduction in the risk of fatal and nonfatal myocardial infarction (MI) for primary prevention, as well as a reduction in CHD death and nonfatal MI and stroke for secondary prevention. Clinical trial results demonstrating that the fibric acid derivatives, as a class, reduce CHD incidence is less robust than that with statin therapy.[11]

Table 1. Current Medications Available in the Therapeutic Class[1-10]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/ Strength	Generic Availability
Fenofibrate (Antara®*, Fenoglide®, Lipofen®, Lofibra®*, Tricor®*, Triglide®)	Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia. Adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, TG and apolipoprotein B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia.	Capsule: 50 mg (Lipofen®) 150 mg (Lipofen®) Capsule, Micronized: 30 mg (Antara®) 43 mg (Antara®) 67 mg (Lofibra®) 90 mg (Antara®) 130 mg (Antara®) 134 mg (Lofibra®) 200 mg (Lofibra®) Tablet: 40 mg (Fenoglide®) 48 mg (Tricor®) 50 mg (Triglide®) 54 (Lofibra®) 120 mg (Fenoglide®) 145 mg (Tricor®) 160 mg (Lofibra®, Triglide®)	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/ Strength	Generic Availability
Fenofibric acid (Fibricor®*, Trilipix®†)	Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fibricor®).‡ Adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, TG and apolipoprotein B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia.	Delayed-release capsule: 45 mg (Trilipix®) 135 mg (Trilipix®) Tablet: 35 mg (Fibricor®) 105 mg (Fibricor®)	✔
Gemfibrozil (Lopid®*)	Treatment of adult patients with very high elevations of serum TG levels who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Reducing the risk of developing CHD only in Type IIb patients without history of or symptoms of existing CHD who have had an adequate response to weight loss, dietary therapy, exercise and other pharmacologic agents and who have the following triad of lipid abnormalities: low HDL-C levels in addition to elevated LDL-C and elevated TG.	Tablet: 600 mg	✔

CHD=coronary heart disease, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, TG=triglycerides
*Generic is available in at least one dosage form and/or strength.
†Choline fenofibrate.
‡Indicated for therapy in patients with triglycerides ≥500 mg/dL.

Evidence-based Medicine

- In general, the fibric acid derivatives consistently demonstrate greater efficacy compared to placebo in the management of hypercholesterolemia and hypertriglyceridemia.[14-18]
- The addition of fibric acid derivatives to other well established lipid lowering agents has been shown to be safe and resulted in additional improvements in lipid profile compared to each drug given as monotherapy.[16-28]
- The five year, placebo-controlled FIELD trial (N=9,975) demonstrated that fenofibrate did not significantly reduce the risk of the combined primary outcome of coronary events (CHD), death or nonfatal myocardial infarction (MI) in patients with type 2 diabetes. When individual endpoints were analyzed, fenofibrate significantly reduced nonfatal MI by 24% (hazard ratio [HR], 0.76; P=0.010), but a nonsignificant increase in CHD mortality (HR, 1.19; P=0.22) was observed.[29] Similar results were observed in the ACCORD trial (N=5,518) which evaluated the efficacy of fenofibrate on reducing the risk of major cardiovascular events in high risk type 2 diabetics.[30]
- In the five year, Helsiniki Heart Study (N=4,081), a primary prevention trial, gemfibrozil demonstrated a significant 34% (P<0.02) reduction in the incidence of cardiac events but demonstrated no effect on all-cause mortality.[31] After 8.5 years of follow up, all-cause mortality was numerically higher with gemfibrozil, but the increase did not meet significance.[32] In a secondary prevention component of the Helsinki Heart Study, there was no difference between gemfibrozil and placebo in the incidence of fatal and nonfatal MI and cardiac death.[33]
- A meta-analysis of 10 randomized controlled trials (N=36,489) evaluated fibric acid derivatives for the primary and secondary prevention of cardiovascular events and demonstrated that treatment tended to increase all-cause mortality (odds ratio [OR], 1.07; P=0.08) and was associated with a significant increase in noncardiovascular mortality (OR, 1.16; P=0.004). No effect of fibric acid derivatives was observed for cardiovascular mortality (OR, 0.98; P=0.68). When the individual fibric acid derivatives were analyzed, the odds of cardiovascular mortality were significantly lower with gemfibrozil (OR, 0.77; P=0.05).[34]

- A second meta-analysis of 18 randomized controlled trials (N=45,058) demonstrated no effect on all-cause mortality (relative risk [RR], 1.00; P=0.918), cardiovascular mortality (RR, 0.97; P=0.582) or sudden death (RR, 0.89; P=0.190). An increased risk of noncardiovascular mortality was noted; however, this finding did not reach significance (RR, 1.10; P=0.063).[35]
- Fenofibric acid was added to rosuvastatin in patients with chronic kidney disease and it was shown that there was a significantly greater decrease in median percent TGs compared to rosuvastatin alone after eight weeks (P<0.001) and 16 weeks (P<0.001) along with an increase in HDL-C over the same time periods (P<0.001).[36]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Therapeutic lifestyle changes remain an essential modality in the management of patients with hypercholesterolemia.[37-46]
    - In general, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are considered first line therapy for decreasing low density lipoprotein cholesterol (LDL-C) levels.
    - Due to increased muscle side effects including rhabdomyolysis, gemfibrozil is not recommended to be used in a combination with statins.[43]
    - Fibric acid derivatives are typically reserved for the treatment of hypertriglyceridemia, to reduce the risk of pancreatitis, or for an isolated low high density lipoprotein cholesterol.[37,40]
    - Fibric acid derivatives can be considered in patients with coronary heart disease who have low levels of LDL-C and atherogenic dyslipidemia, or in combination with a statin in patients who have elevated LDL-C and atherogenic dyslipidemia.[37] Since the publication of these guidelines, the FD) requested the discontinuation of the marketing of Trilipix® indicated as an adjunct to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD (coronary heart disease) or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal. This decisions was based on the FDA's conclusion that the totality of the scientific evidence no longer supports the conclusion that a drug-induced reduction in TG and/or increase in HDL-C levels in statin-treated patients results in a reduction in the risk of cardiovascular events.[47]
    - The National Institute for Health and Clinical Excellence (NICE) guidelines recommend non-routine use of fibrates if intolerant to statins as monotherapy and recommend against the use of niacin, bile acid sequestrants, and omega-3 fatty acids or any combination of a stains plus either a fibrate, niacin, bile acid sequestrants, or omega-3 fatty acids for primary or secondary prevention of coronary vascular disease due to lack of evidence.[44]

- Other Key Facts:
    - Gemfibrozil (Lopid®) is the only fibric acid derivative approved for reducing the risk of developing coronary heart disease in select patients.[10]
    - Currently, all fibric acid derivatives are available generically in at least one dosage form and/or strength.[12]

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