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Indiana Medicaid Therapeutics Committee **Therapeutic Class Review Summary**

Therapeutic Class:
Fibric Acid Derivatives

Overview:

Clofibrate, approved by the FDA in 1967, was the first fibric acid derivative introduced in the United States for the treatment of hyperlipidemia. However, it was discontinued due to serious side effects (hepatic tumors, cholelithiasis, cholecystitis, and pancreatitis). The currently available fibric acid derivatives are gemfibrozil (FDA approved in 1981), fenofibrate, and fenofibric acid. Micronized fenofibrate was first introduced as a capsule (TriCor® 67 mg, 134 mg, and 200 mg) in 1998. In 2001, a tablet formulation (54 mg and 160 mg) was approved and replaced the capsules. The tablet was able to achieve the same concentration of drug in the blood as the capsule but at lower doses. Reformulated TriCor® tablets (48 mg and 145 mg) were approved in November 2004. The new tablets achieve the same drug concentrations in the plasma, are still administered once daily, and, unlike the prior formulations, can be taken without regard to meals. Dosage reduction is recommended in patients with mild to moderate renal impairment receiving Tricor. Antara™ capsules (43 mg, 87 mg and 130 mg) were approved late November 2004, and Triglide™ tablets (50 mg and 160 mg) were approved May 2005. Like the reformulated TriCor® tablets, Triglide™ tablets may be given without regard to meals. Generic products have been approved for the fenofibrate 67-, 134-, and 200-mg capsules and fenofibrate 54- and 160-mg tablets. However, the availability of the generic products has been inconsistent. Trilipix™ or fenofibric acid, which is the active metabolite of fenofibrate, received FDA approval in December 2008, and is available in 45- and 135-mg delayed release capsules. Fibracor™, also fenofibric acid, received FDA approval in August 2009 and is available in 35- and 105- mg tablets. Both are indicated to reduce triglycerides (TG) in patients with severe hypertriglyceridemia, and to reduce elevated low density lipoprotein cholesterol (LDL-C), total cholesterol (TC), TG, and apolipoprotein B, and to increase high density lipoprotein cholesterol (HDL-C) in patients with primary hyperlipidemia or mixed dyslipidemia. In addition, Trilipix™ is approved for use in combination with a statin to reduce triglycerides and increase HDL-C in patients with mixed dyslipidemia and coronary heart disease (CHD) or a CHD risk equivalent that are on optimal statin therapy.

Gemfibrozil decreases serum triglycerides and very low-density lipoprotein (VLDL) cholesterol and increases HDL-C. Gemfibrozil exerts its action by inhibiting peripheral lipolysis and decreasing the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. Gemfibrozil also inhibits the synthesis and increases the clearance of apolipoprotein B, a carrier molecule for VLDL. The mechanism for increased HDL levels is unknown. With gemfibrozil therapy, modest decreases in total and LDL-C may be observed, except in type IV hyperlipoproteinemia (patients often

experience a rise in LDL) and in type IIb (patients experience minimal effects on LDL levels but usually show significant increases in HDL).

Fenofibrate is a prodrug that is hydrolyzed to fenofibric acid, the active moiety. Fenofibric acid reduces total cholesterol, LDL cholesterol, apolipoprotein B (apo B), total triglycerides, and triglyceride-rich particles (VLDL). Moreover, treatment with fenofibrate results in increases in HDL and apolipoproteins A-I and A-II (apoAI, apoAII). Fenofibric acid increases lipolysis and the elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity). The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles, which are thought to be atherogenic because of their susceptibility to oxidation, to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Fenofibrate also reduces serum uric acid levels by increasing the urinary excretion of uric acid.

The fibric acid derivatives are most effective in treating lipid disorders associated with very high elevations of serum triglycerides and VLDL (type IV and V hyperlipoproteinemia). Fenofibrate appears to reduce LDL to a greater extent than gemfibrozil, but this observation has not yet been confirmed by comparative clinical trials. The only published head-to-head trial used a lower than recommended dose of gemfibrozil.

The most frequently reported adverse effects associated with fibric acid derivatives are GI related: abdominal pain, dyspepsia, nausea/vomiting, diarrhea, and cholestasis with jaundice. Cholelithiasis, cholecystitis, myopathy, myositis, and dermatologic reactions (fenofibrate) may also occur. Concomitant use of fibric acid derivatives with a HMG CoA reductase inhibitor is associated with an increased risk of myopathy and rhabdomyolysis. Combination therapy should be avoided when possible.

Generic Name	Brand Name	Manufacturer	Generic Available
Fenofibrate capsules 67 mg, 134 mg, 200 mg	Lofibra™	Gate Pharmaceuticals, various	Yes
Fenofibrate capsules 43 mg and 130 mg	Antara™	Reliant Pharmaceuticals	No
Fenofibrate 40mg and 120mg	Fenoglide™	Lifecycle Pharma	No
Fenofibrate tablets 54 mg and 160 mg	Lofibra™	Gate Pharmaceuticals, various	Yes
Fenofibrate tablets 48 mg and 145 mg ¹	TriCor®	Abbott	No
Fenofibrate tablets	Triglide™	SkyePharma	No



50 mg and 160 mg			
Fenofibrate tablets 50 mg and 150 mg	Lipofen™	ProEthic	No
Fenofibric Acid 35mg and 105mg	Fibricor™	AR Holding Co	No
Fenofibric Acid 45mg and 135mg	Trilipix™	Abbott	No
Gemfibrozil 600 mg	Lopid®	Pfizer, various	Yes

¹ The brand 54-mg and 160-mg TriCor tablets have been discontinued and replaced with the reformulated 48-mg and 145-mg TriCor tablets.

Summary:

The fibric acid derivatives play an important role in the treatment of hypercholesterolemia where reducing triglycerides and/or increasing HDL-C are of primary importance. The two agents available in the US are probably clinically equivalent. The one head-to-head comparison used a lower than recommended dose of gemfibrozil. Although the availability of the generic products has been inconsistent, both gemfibrozil and fenofibrate are available generically. Fenofibric acid, the active metabolite of fenofibrate, has been approved in a delayed release capsule formulation which is approved for use in combination with a statin, and most recently in a tablet formulation. Selection of an agent for the preferred drug list should be based upon efficacy, safety, and total cost impact to the program.