

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 two currently available fibric acid derivatives are gemfibrozil (FDA approved in 1981) and fenofibrate. 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 and 130 mg) were approved late November 2004, Triglide[™] tablets (50 mg and 160 mg) were approved May 2005, and Lipofen[™] capsules (50mg and 150mg) were approved in January 2006. 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.

Gemfibrozil decreases serum triglycerides and very low-density lipoprotein (VLDL) cholesterol and increases high-density lipoprotein (HDL) cholesterol. 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 low-density lipoprotein (LDL) cholesterol 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, 13 mg, 200 mg	Lofibra™	Gate Pharmaceuticals, various	Yes
Fenofibrate capsules 43 mg and 130 mg	Antara™	Reliant Pharmaceuticals	No
Fenofibrate tablets 54 mg and 160 mg	----	Ranbaxy, Teva, Par, Impax, Lifecycle	Yes
Fenofibrate tablets 48 mg and 145 mg ¹	TriCor®	Abbott	No
Fenofibrate tablets 50 mg and 160 mg	Triglide™	SkyePharma	No
Fenofibrate capsules 50mg, 150mg	Lipofen™	Cipher Pharmaceuticals	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. Selection of an agent for the preferred drug list should be based upon the total cost impact to the program.