Indian Health Service
IHS National Pharmacy and Therapeutics Committee
Dyslipidemia Update Part II (Fibrates, Ezetimibe, BAS)
April 2012

Objectives:

1. Support the national pharmacy and therapeutics committee by giving current clinical data on fibrates, Bile Acid Sequestrants (BAS), and ezetimibe.
2. Provide current primary literature addressing each class of medications.
3. Make recommendations to the IHS National Pharmacy and Therapeutics Committee (NPTC) based on the available clinical evidence.

Introduction:

According the IHS Fact Sheet, "Diseases of the heart, malignant neoplasm, unintentional injuries, diabetes, and cerebrovascular disease are the five leading causes of Indian deaths (2004-2006)."[1] High cholesterol levels are a contributor to heart disease and death. The purpose of this review is to support the IHS NPTC with making any necessary adjustments to the IHS National Core Formulary (NCF). This overview will consist of two drug classes, fibric acid derivatives (fibrates) and BAS, along with the drug ezetimibe. Currently, gemfibrozil is the only medication on the core formulary.

Guidelines Summary:

The National Cholesterol Education Program – Adult treatment Panel III (NCEP ATP III) guidelines recommend lowering LDL as the primary goal with Non-HDL as a secondary goal in the management of dyslipidemia. HMG-CoA reductase inhibitors (statins) remain the backbone of pharmacotherapy due to their potent ability to lower cholesterol levels. Along with statins, niacin, and BAS are also used to lower LDL. Triglycerides may become the primary goal when elevated to ≥ 500 mg/dL due the patients increase risk of acute pancreatitis. Pharmacotherapy should utilize triglyceride-lowering agents such as fibrates or nicotinic acids. The NCEP ATP III guidelines have set cholesterol goals based on the patient's risk factors (see table 1). The NCEP update in 2004 stated that some patients with an LDL goal of <100mg/dL may need duel therapy to reach their goal. Statins are the base of therapy with the second agent being ezetimibe, BAS, nicotinic acid, or plant stanols/sterols.[2] The NCEP ATP IV guidelines are expected to be released this year, 2012.[3]

Table 1: Management Based Upon Risk[3]

Patient Risk	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Initiate Drug Therapy (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)
Highest-risk patients **1) CHD** **2) CHD risk equivalents (eg, diabetes, peripheral vascular disease, a Framingham 10-year risk estimate >20%)**	< 100 (<70 if very high risk)	1) < 100 2) < 130	≥ 130 (100-129 mg/dL drug option)	Low HDL-C < 40 mg/dL Consider raising HDL in high-risk individuals regardless of TG levels (niacin or fibrate)	TG ≥ 500 primary target
Moderate high-risk patients ≥ 2 risk factors and Framingham 10-year risk estimate 10%-20%	< 130	< 160	≥ 130		
Moderate risk patients ≥ 2 risk factors and Framingham 10-year risk estimate <10%	< 130	< 160	≥160		

Low risk patients **0-1 risk factor**	< 160	< 190	≥ 190 (160-189 LDL-lowering drug optional)		

CHD: history of MI, unstable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia
Risk Factors: cigarette smoking, hypertension (BP ≥140/90 mmHG or on antihypertensive medication), low HDL, family history (first degree relative male <55 years of age or female <65 years of age), and the patients age (men ≥45 years and women ≥55 years)

Fibrates

Background

Fibrates act to lower cholesterol in the body by reducing the rate of lipogenesis in the liver. Fenofibric acid derivatives are work through a long process. They are agonists for the nuclear transcription factor peroxisome proliferator-activated receptor-alpha (PPAR-alpha) which downregulates apoprotein C-III (an inhibitor of lipoprotein lipase). Then an upregulation of the synthesis of apolipoprotein A-1, fatty acid transport protein, and lipoprotein lipase occur. This upregulation results in an increase in VLDL catabolism, fatty acid oxidation, and elimination of triglyceride-rich particles. Gemfibrozil's exact mechanism is unknown. It is theorized that it inhibits lipolysis and decreased hepatic fatty acid uptake as well as inhibit hepatic secretion of VLDL and subsequently decreases VLDL levels.[3,4]

FDA-approved indications

Gemfibrozil[5]

- Treatment of adults with hypertriglyceridemia in Fredrickson (types IV and V)
- Reducing risk of developing CHD in Fredrickson Type IIb patients without history or symptoms of existing CHD without response from diet, exercise or other prescription medications (niacin or BAS), and who have decreased HDL levels, elevated LDL and elevated TG levels.

Fenofibrates[4,6,7]

- Treatment of adults with primary hypercholesterolemia or mixed dyslipidemia (types IIa and IIb)
- Treatment of hypertriglyceridemia in adult patients with Fredrickson Types IV and V hyperlipidemia
- Fenofibric acid indicated for co-administration therapy with statins for the treatment of mixed dyslipidemia

Pharmacokinetics

Gemfibrozil[5]

- Absorption: well absorbed from the GI tract
- Distribution: 99% protein bound
- Metabolism: Hepatic via oxidation to two inactive metabolites which undergo enterohepatic recycling
- Excretion: Urine ~70%; feces 6%
- Onset of action: May require several day
- Half-life: 1.5 hours
- Time to peak: 1-2 hours

Fenofibrates[4,6,7]

- Absorption: Increased when taken with meals
- Distribution: widely to most tissues with >99% protein binding
- Metabolism: Tissue and plasma via esterases to active form, fenofibric acid
- Excretion: Urine 60%; feces 25%
- Half-life: average 20 hours (10-35 hours)
- Time to peak: 3-8 hours

Table 2: Fibrate Dosing[4-7]

Drug	Brand Name	Dose
Gemfibrozil	Lopid	600 mg twice daily
Fenofibrate	Tricor	48-145 mg daily
Fenofibric acid	Trilipix	45-135 mg daily

Fibrates lower triglycerides by 30%-60% and raise HDL 18%-22%. The LDL lowering potential is dependent upon the patient's triglyceride level. For a patient with normal triglycerides, the LDL lowering expectancy is between 5%-20%. For a patient with very high triglycerides, a raise in LDL up to 45% can be seen.[4-7]

The adverse effects seen with fibrates include: dyspepsia, gallstones, myopathy, and increased hepatic transaminases (dose related). Monitoring includes liver function tests (LFTs) every 3 months during the first year and then periodically. This class of medications is contraindicated in patients with severe hepatic or renal disease and pre-existing gallbladder disease.[4-7]

New FDA Labeling:
Recent drug interaction information has been released by the FDA in regarding the use of statins with a variety of medications including gemfibrozil. Current common drug interactions are below.[5-7]

Table 3: Fibrate Drug Interactions[5-7]

	Avoid Concomitant Use	May Increase level/effect	May decrease level/effect
Gemfibrozil	Simvastatin, Lovastatin, Clopidogrel, Repaglinide	Atorvastatin, Pravastatin, Rosuvastatin, Lovastatin Carvedilol, Citalopram, Colchicine, Ezetimibe, Sulfonylureas, Vitamin K Antagonists, Warfarin	Clopidogrel, Cyclosporin, Chenodiol
Fenofibrate	None	HMG-CoA reductase Inhibitors, Ezetimibe, Sulfonylureas, Vitamin K Antagonists, Warfarin	Cyclosporin, Chenodiol
Fenofibric acid			

Efficacy:
Several clinical trials have been published that evaluate the efficacy of fibrates and demonstrates a benefit in lowering triglyceride levels and raising HDL. A reduction in the progression of coronary lesions has been seen as well as a reduction in major coronary events. [4-7]

Helsinki Heart Study (HHS) was a randomized, double blind five year trial in which 4081 asymptomatic middle aged men with dyslipidemia were randomized to receive either gemfibrozil or placebo for five years. Gemfibrozil increased HDL and decreased LDL in the treatment group. Incidence of coronary artery disease of was reduced by 34 percent. A follow-up analysis revealed that the treatment group had a 32% reduction in coronary mortality.[8]

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study was a randomized, double blind, placebo controlled trial with 9795 participants with type 2 diabetes that were randomized to receive either fenofibrate or placebo. At the conclusion of the trial, fenofibrate did not show a significant decrease in coronary events. However, a significant reduction in non-fatal myocardial infarction was seen. There has been recent discussion on the possible masking of fenofibrates benefit in the analysis due to statin use in the placebo group.[9]

The ACCORD-Lipid trial randomly assigned 5518 patients with type 2 diabetes, who were being treated with open-label simvastatin, to receive either masked fenofibrate or placebo. The primary endpoints were the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. Analysis revealed no significant differences between the two groups in regards to the primary outcomes. The baseline plasma cholesterol levels proved to be a major limitation to the study. The average starting lipid panel was as follows: Total 175 mg/dL, LDL 100 mg/dL, and HDL 38 mg/dl, and triglycerides 162 mg/dl. A subgroup analysis saw an increase in increase in cardiovascular events in women. The clinical significance of the finding was unclear.[10]

An additional subgroup analysis suggested a possible fenofibrate benefit for moderate dyslipidemic patients with both a high baseline triglyceride level (TG≥204 mg/dl) and low HDL (≤ 34 mg/dl). This subgroup with moderate dyslipidemia comprised 941 individuals or 17.6% of the total population within the trial. The primary outcome rate was 12.37% in the fenofibrate group (n=485) and 17.32% in the placebo group (n=456). This represents a crude 28% or adjusted 31% relative risk reduction. Since this subgroup comprised such a small part of the entire population, the results were likely diluted by the larger cohort with lower baseline characteristics.[11]

A meta-analysis of five major randomized clinical trials (HHS, VA-HIT, BIP, Field, and ACCORD-Lipid) provided a larger population of moderate dyslipidemia participants. The analysis revealed fenofibrate benefits in the following patient groups: "low HDL only" patients had reduced CVD events by 17% (P<0.001), "hypertriglyceridemia-only" patients reduced CVD events by 28% (P, 0.001), and "atherogenic (moderate) dyslipidemia" phenotype reduced CVD events by 30% (P<0.0001). Analysis of patients with diabetes on fibrate therapy also demonstrated a significant benefit in microvascular outcomes such as retinopathy and nephropathy that could be independent of lipid levels.[11]

A head to head trial was conducted to compare the effects of micronized fenofibrate and gemfibrozil in a multicenter, double-blind, randomized 24-week study with 234 patients with combined hyperlipidemia. Patients were randomized to fenofibrate at 200mg per day and gemfibrozil 1200mg per day. The outcomes revealed no difference in lipid lowering between both groups. Triglycerides decreased 39-41%.[12]

No head to head trials have been conducted comparing the different fenofibrate formulations. The newest formulations were approved by the FDA by demonstrating bioequivalence to fenofibric acid.

Conclusions:

Several clinical trials have been conducted to evaluate the efficacy of fibrates. Fibrates show a benefit by lower triglycerides and raising HDL. Drug interactions with gemfibrozil should be taken into consideration when considering its use.

Ezetimibe

Background:

There have been several studies that evaluated the LDL-C lowering benefit of ezetimibe when added to statins. The addition of ezetimibe can results in a 12-15% reduction in LDL-C with a 20% response seen in some patients.[13,14] Ezetimibe is the first of its class of cholesterol lowering medications. Ezetimibe is not on the IHS NCF.[15]

Recent studies have evaluated the clinical benefit of ezetimibe. Recent published data suggests the clinical benefit of ezetimibe is in question.[13,14] The ATP IV guidelines are expected to be released this year and address ezetimibe's place in therapy. Recently, the FDA decided not to approve the combination drug atorvastatin/ezetimibe stating that further data was needed.[16]

Pharmacology/Pharmacokinetics:[17]

Pharmacology:

- Selectively inhibits absorption of cholesterol (dietary and biliary) at the brush border of the small intestines which leads to a decrease in the delivery of intestinal cholesterol to the liver. The liver in turn uses hepatic cholesterol stores and increases the clearance of cholesterol from the blood.

Table 4: Ezetimibe Pharmacokinetics[17]

Pharmacokinetic Parameter	
Absorption	• Absorbed and extensively conjugated to active phenolic glucuronide • Food had no effect on absorption • Average peak plasma concentrations of ezetimibe are reached within 4-12 hours and ezetimibe-glucuronide within 1-2 hours
Distribution	• 99% bound to plasma proteins
Metabolism	• Undergoes glucuronide conjugation in the small intestine and forms an active metabolite ezetimibe-glucuronide which is 80-90% of total drug in plasma • Ezetimibe is also active accounting for 10-20% of total drug in plasma • May undergo enterohepatic recycling
Excretion	• Feces 78% • Urine 11% • Half-life 22 hours

FDA Approved Indications: [17]

- Reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with primary hyperlipidemia, alone or in combination with an HMG-CoA reductase inhibitor
- Reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia in combination with an HMG-CoA reductase inhibitor

Dosage and Administration: [17]

Ezetimibe 10mg tablet by mouth once daily, with or without food
Dosing should occur ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant.

Efficacy:

The LDL-C lowering potential of ezetimibe is well established. Several clinical trials have been performed.[18-20]

Table 5: Relevant Ezetemibe Clinical Trials

Clinical Trial	Trial Details	Results
Gagne, et al[18]	Multicenter, randomized, double blind, placebo controlled trial 769 patients with primary hypercholesterolemia currently on statin medication, but not at LDL-C goal. Baseline LDL-C: 139 mg/dL Patients received ezetimibe 10mg or placebo in addition to their current open-label statin	% from baseline LDL: Ezetimibe -25.1, Placebo -3.7 HDL: Ezetimibe +2.7, Placebo +1 TG: Ezetimibe -14, Placebo -2.9 LDL P<0.001 TG P<0.05 Resulted in a 21% reduction in combination with statin therapy
Lipka, et al[19]	Multicenter, randomized, double blind, placebo controlled trial 1861 patients with primary	%LDL-C lowering favored combination therapy. <65: -12.8 ≥65: -15.5 <75: -13.5 ≥75: -14.5

<table>
<tr><td></td><td>hypercholesterolemia. Baseline LDL-C 178 mg/dL

Patients were randomized one of the following groups: placebo, statin, ezetimibe+statin (statins included lovastatin, atorvastatin, simvastatin)</td><td>Combination therapy
• reduced TG 27-29% vs. 16-20% statin only
• Increased HDL-C by 8-11% vs. 5-6% statin only</td></tr>
<tr><td>Ballantyne, et al[20]</td><td>Randomized, double blind, placebo controlled trial

628 patients with primary hypercholesterolemia. Baseline LDL-C 175-184 mg/dL

Patients were randomized one of the following groups: placebo, ezetimibe 10mg, atorvastatin 10-80mg, atorvastatin 10-80mg +ezetimibe</td><td>% Change from baseline (p<0.01)
<table>
<tr><td></td><td>LDL</td><td>HDL</td><td>TG</td></tr>
<tr><td>Placebo</td><td>5.9</td><td>3.7</td><td>-6.4</td></tr>
<tr><td>Ezetimibe</td><td>-18.4</td><td>+4.2</td><td>-5.1</td></tr>
<tr><td>Atorvastatin</td><td>-42.4</td><td>+4.3</td><td>-24.5</td></tr>
<tr><td>Atorv+Ezet</td><td>-54.5</td><td>+7.3</td><td>-32.8</td></tr>
</table>
Combination provided an additional 12.1% reduction in LDL-C and was the favor over all comparison groups (LDL,HDL,TG).</td></tr>
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Recent trials have been released questioning the clinical benefit of ezetimibe. Two in particular are The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial and the Arterial Biology for the investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER-6) trial. [13,14]

Both of these trials look at a surrogate marker, carotid artery intima-media thickness, and not a clinical outcome as the primary endpoint. Carotid artery intima-media thickness has been strongly associated with atherosclerosis and cardiovascular events.[21]

The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial was a double-blind, randomized, 24-month trial. This earlier trial had a primary endpoint of mean change in carotid artery intima-media thickness (CA IMT). It was a double-blind, randomized, 24 month trial comparing the effects of combination therapy of ezetimibe 10mg and simvastatin 80mg to simvastatin 80mg monotherapy. The results pointed to no significant difference (P=0.29) in the CA IMT in the treatment group regardless of additional LDL-C and C-reactive protein lowering.[13]

Table 6: ENHANCE Data[13]

Group	Change in CA IMT (mm)	P Value
Simvastatin only	0.0058 ± 0.0037	P=0.29
Simvastatin + Ezetimibe	0.0111 ± 0.0038	P=0.29

Arterial Biology for the investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis trial (ARBITER-6) was a randomized trial that compared niacin therapy to ezetimibe in patients on a stable statin treatment. The primary endpoint was change in mean carotid intima-media thickness (CA IMT). The trial was terminated early due to pre-analysis showing superiority of niacin over ezetimibe on change in CA IMT. Niacin significantly reduced the mean and maximal CA IMT. Ezetimibe did not show a significant reduction in mean or maximal CA IMT.[14]

Table 7: ARBITER-6 Data

Group	Change in CA IMT (mm)	P Value

Niacin	0.0102 ± 0.0026	P<0.001
Ezetimibe	0.0016 ± 0.0024	P<0.88

The Examining Outcome in Subjects with Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) vs Simvastatin (IMPROVE-IT) trial is ongoing with results expected in 2013.[22]

Conclusions:
Ezetimibe is the first member of the new class of cholesterol lowering medications. It has shown an ability to lower LDL-C by up to 20% compared to statins alone. Despite its ability to lower LDL-C, ezetimibe has not shown a benefit in reducing CA IMT.

Bile Acid Sequestrants

Background:
Bile Acid Sequestrants (BAS) medications lower cholesterol levels by binding to bile acids and disrupting enterohepatic recirculation of bile acids. The liver is then stimulated to convert hepatocellular cholesterol to bile acids. This class of medications should be taken either 30 prior to a meal or 4 to 6 hours following a meal. NCEP ATP III guidelines recommend BAS as adjunct therapy with statins in patients with very high LDL or as an alternative to statins for the management of dyslipidemia. NCEP also has additional recommendations for use in patients with moderately elevated LDL, women who are considering pregnancy and have elevated LDL, and patients who need only modest reductions in order to reach their LDL cholesterol goal. [3,23-25]

FDA Approved Indications:
Cholestryramine[25]
- Adjunct management of primary hypercholesterolemia
- Pruritus associated with elevated levels of bile acids
- Regression of arteriolosclerosis
- Unlabeled use of diarrhea associated with excess fecal bile acids and enhanced elimination of digoxin when non-life-threatening toxicity occurs

Colestipol[24]
- Adjunct management of primary hypercholesterolemia
- Unlabeled use in diarrhea associated with excess fecal bile acids and relief of pruritus associated with elevated levels of bile acids

Colesevelam[23]
- Management of elevated LDL in primary hypercholesterolemia (Fredrickson type IIa) when used alone or in combination with an HMG-CoA reductase inhibitor
- Management of heterozygous familial hypercholesterolemia (heFH) in adolescent patients (males and postmenarcheal females 10-17 years of age) when used alone or in combination with an HMG-CoA reductase inhibitor
- Patients who after an adequate trial of dietary therapy have LDL-C≥190 mg/dL or LDL-C≥160 mg/dl with positive family history of premature cardiovascular disease (CVD) or with two or more CVD risk factors, improve glycemic control in type 2 diabetes mellitus (noninsulin dependent, NIDDM) in conjunction with diet, exercise, and insulin or oral antidiabetic agents.

Pharmacokinetics:[23-25]
- Absorption: None
- Excretion: Feces

Table 8: Bile Acid Sequestrants[23-25]

Drug	Brand	Usual Dosage Range
Cholestryramine	Questran	4-16 grams/day
Colestipol	Colestid	5-20 grams/day
Colesevelam	WelChol	2.6-3.8 grams/day

Table 9: Dose-Dependent Effects on BAS on LDL-C Concentrations [23-25]

	Dose (g)	% LDL-C Reduction
Cholestyramine	4-8	-9
	8-12	-13
	12-16	-17
	16-20	-21
	20-24	-28
Colestipol	5	-12
	10	-20
	15	-24
Colesevelam	3.8	-15
	4.5	-18

A dose-dependent LDL reduction of approximately 15%-26% along with an HDL increase of approximately 3%-6% has been observed. An increase in triglycerides may be seen. Reductions in major coronary events and CHD mortality have been reported. [12]

Reported adverse effects include gastrointestinal related including distress and constipation. BAS can decrease the absorption of other medications including: warfarin, beta-blockers, and thiazides. To reduce possible drug interactions administer other medications 1-2 hours before or 4 hours after a bile acid sequestrant. This medication is contraindicated in patients with dysbetalipoproteinemia and increased triglyceride concentrations (especially greater than 400 mg/dL). [12]

Efficacy:
The benefit that bile acid sequestrants (BAS) can have on LDL and HDL were demonstrated in the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT). This was a placebo-controlled trial in which 3806 men with primary hypercholesterolemia either given placebo or 24g/d cholestyramine. Compared to placebo, cholestyramine demonstrated a 19% reduction in combined rate of coronary heart disease death and nonfatal myocardial infarction relative to placebo. Cholestyramine also resulted in a reduction in triglycerides (17% vs 1%) and LDL (26% vs 5%).[26,27]

The National Heart, Lung, and Blood Institute (NHLBI) Type II Coronary Intervention Study compared cholestyramine to placebo in 143 patients. The patients were assigned to receive cholestyramine or placebo. Cholestyramine reduced LDL to a greater degree than placebo (26% vs. 5%). The changes in HDL and triglycerides were not significant. [29]

No adequately powered head to head trials have been performed to evaluate the benefit of one BAS over another.

Conclusions:
Bile acid sequestrants show a benefit by lowering LDL-C. With no adequately powered head to head trials, dosing and tolerability should be considered when prescribing these medications.

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