



**Indian Health Service  
National Pharmacy and Therapeutics Committee**

**Ezetimibe  
April 2012**



**Introduction:**

According to 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).”<sup>1</sup> High cholesterol levels are a contributor to heart disease and death. 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. HMG-CoA reductase inhibitors (statins) remain the backbone of pharmacotherapy due to their potent ability to lower cholesterol levels. Along with statins, niacin and bile acid sequestrants are also used to lower LDL. 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 dual therapy to reach their goal. Statins are the base of therapy with the second agent being ezetimibe, BAS, nicotinic acid, or plant stanols/sterols.<sup>2</sup> The NCEP ATP IV guidelines are expected to be released this year, 2012.<sup>3</sup>

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**Table 1: Management Based Upon Risk<sup>3</sup>**

Patient Risk**	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Initiate Drug Therapy (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)
<b>Highest-risk patients</b> 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
<b>Moderate high-risk patients</b> ≥ 2 risk factors and Framingham 10-year risk estimate 10%-20%	< 130	< 160	≥ 130		
<b>Moderate risk patients</b> ≥ 2 risk factors and Framingham 10-year risk estimate <10%	< 130	< 160	≥ 160		
<b>Low risk patients</b> 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

Note: Information within this document is current as of this writing and should not replace clinical judgment

\*\*Risk Factors: cigarette smoking, hypertension (BP  $\geq$ 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  $\geq$ 45 years and women  $\geq$ 55 years)

There have been several studies that evaluated the LDL-C lowering benefit of ezetimibe when added to statins. The combination of ezetimibe and a statin can result in an additional 12-15% reduction in LDL-C with a 20% response seen in some patients. More recent studies have evaluated the clinical benefit of ezetimibe. These studies show that despite a lowering of LDL-C, clinical benefit is lacking.<sup>3-5</sup>

Recent published data suggests the clinical benefit of ezetimibe is in question.<sup>4,5</sup> Recently, the FDA decided not to approve the combination drug atorvastatin/ezetimibe stating that further data was needed.<sup>6</sup>

### **Pharmacology/Pharmacokinetics:**<sup>7,8</sup>

Pharmacology:

- Selectively inhibits absorption of cholesterol (dietary and biliary) at the brush border of the small intestines leading 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 2: Pharmacokinetics**<sup>7,8</sup>

Pharmacokinetic Parameter	
<b>Absorption</b>	<ul style="list-style-type: none"> <li>• Absorbed and extensively conjugated to active phenolic glucuronide</li> <li>• Food had no effect on absorption</li> <li>• Average peak plasma concentrations of ezetimibe are reached within 4-12 hours and ezetimibe-glucuronide within 1-2 hours</li> </ul>
<b>Distribution</b>	<ul style="list-style-type: none"> <li>• 99% bound to plasma protein</li> </ul>
<b>Metabolism</b>	<ul style="list-style-type: none"> <li>• Undergoes glucuronide conjugation in the small intestine and forms an active metabolite ezetimibe-glucuronide which is 80-90% of total drug in plasma</li> <li>• Ezetimibe is also active accounting for 10-20% of total drug in plasma</li> <li>• May undergo enterohepatic recycling</li> </ul>
<b>Excretion</b>	<ul style="list-style-type: none"> <li>• Feces 78%</li> <li>• Urine 11%</li> <li>• Half-life 22 hours</li> </ul>

### **FDA Approved Indications:**<sup>7</sup>

- 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

### **Current National Core Formulary Alternatives:**<sup>9</sup>

Ezetimibe is the first of its class of cholesterol lowering medications. Currently, ezetimibe is not on the IHS National Core Formulary.

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**Dosage and Administration:** <sup>7</sup>

Ezetimibe 10mg tablet by mouth once daily, with or without food

Dosing should occur  $\geq 2$  hours before or  $\geq 4$  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 and are enumerated in Table 3.

**Table 3: Relevant Clinical Trials**

Clinical Trial	Trial Details	Results																				
<b>Gagne, et al</b> <sup>10</sup>	<p>Multicenter, randomized, double blind, placebo controlled trial</p> <p>769 patients with primary hypercholesterolemia currently on statin medication, but not at LDL-C goal. Baseline LDL-C: 139 mg/dL</p> <p>Patients received ezetimibe 10mg or placebo in addition to their current open-label statin</p>	<p>% from baseline</p> <table border="1"> <thead> <tr> <th></th> <th>LDL</th> <th>HDL</th> <th>TG</th> </tr> </thead> <tbody> <tr> <td>Ezetimibe</td> <td>-25.1</td> <td>+2.7</td> <td>-14</td> </tr> <tr> <td>Placebo</td> <td>-3.7</td> <td>+1</td> <td>-2.9</td> </tr> </tbody> </table> <p>LDL P&lt;0.001 TG P&lt;0.05</p> <p>Resulted in a 21% reduction in combination with statin therapy</p>		LDL	HDL	TG	Ezetimibe	-25.1	+2.7	-14	Placebo	-3.7	+1	-2.9								
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<b>Lipka, et al</b> <sup>11</sup>	<p>Multicenter, randomized, double blind, placebo controlled trial</p> <p>1861 patients with primary hypercholesterolemia. Baseline LDL-C 178 mg/dL</p> <p>Patients were randomized one of the following groups: placebo, statin, ezetimibe+statin (statins included lovastatin, atorvastatin, simvastatin)</p>	<p>%LDL-C lowering favored combination therapy.</p> <table border="1"> <thead> <tr> <th>&lt;65</th> <th><math>\geq 65</math></th> <th>&lt;75</th> <th><math>\geq 75</math></th> </tr> </thead> <tbody> <tr> <td>-12.8</td> <td>-15.5</td> <td>-13.5</td> <td>-14.5</td> </tr> </tbody> </table> <p>Combination therapy</p> <ul style="list-style-type: none"> <li>reduced TG 27-29% vs. 16-20% statin only</li> <li>Increased HDL-C by 8-11% vs. 5-6% statin only</li> </ul>	<65	$\geq 65$	<75	$\geq 75$	-12.8	-15.5	-13.5	-14.5												
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<b>Ballantyne, et al</b> <sup>12</sup>	<p>Randomized, double blind, placebo controlled trial</p> <p>628 patients with primary hypercholesterolemia. Baseline LDL-C 175-184 mg/dL</p> <p>Patients were randomized one of the following groups: placebo, ezetimibe 10mg, atorvastatin 10-80mg, atorvastatin 10-80mg +ezetimibe</p>	<p>% Change from baseline (p&lt;0.01)</p> <table border="1"> <thead> <tr> <th></th> <th>LDL</th> <th>HDL</th> <th>TG</th> </tr> </thead> <tbody> <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> </tbody> </table> <p>Combination provided an additional 12.1% reduction in LDL-C and was the favor over all comparison groups (LDL, HDL, TG).</p>		LDL	HDL	TG	Placebo	5.9	3.7	-6.4	Ezetimibe	-18.4	+4.2	-5.1	Atorvastatin	-42.4	+4.3	-24.5	Atorv+Ezet	-54.5	+7.3	-32.8
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Recent trials have been published that question 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.<sup>4,5</sup> Both of these trials look at a surrogate marker, carotid artery intima-media thickness, as the primary endpoint. Carotid artery intima-media thickness has been strongly associated with atherosclerosis and cardiovascular events, however, the use of a surrogate end-point must be taken into consideration.<sup>13</sup>

The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial was an early trial with 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 statistically significant difference (P=0.29) in the CA IMT in the treatment group regardless of additional LDL-C and C-reactive protein lowering.<sup>2</sup>

**Table 4: ENHANCE Data<sup>2</sup>**

Group	Change in CA IMT (mm)	P Value
Simvastatin –only	0.0058 ± 0.0037	P=0.29
Simvastatin and 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 open-labeled therapy with niacin 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.<sup>3</sup>

**Table 5: ARBITER-6 Data<sup>3</sup>**

Group	Change in CA IMT (mm)	P Value
<b>Niacin</b>	0.0102 ± 0.0026	P<0.001
<b>Ezetimibe</b>	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.<sup>14</sup>

**Adverse Events:**<sup>8</sup>

Central nervous system: Fatigue (2%)

Gastrointestinal: Diarrhea (4%)

Neuromuscular & skeletal: Arthralgia (3%), pain in extremity (3%)

Respiratory: Upper respiratory tract infection (4%), sinusitis (3%)

**Precautions/Contraindications:** <sup>7</sup>

Ezetimibe is not recommended in patients with moderate or severe hepatic impairment. Contraindicated in the following:

- Hypersensitivity to any component within ezetimibe
- Statin contraindications apply when used in combination
  - Active liver disease
  - Pregnancy or may become pregnant
  - Nursing mothers

**Look-alike/Sound-alike Error Risk Potential:** <sup>15,16</sup>

Potential error exists with Zetia <sup>®</sup> and the following drug names: Bextra <sup>®</sup>, Zebeta <sup>®</sup>, Zestril <sup>®</sup>

The VA PBM and Center for Medication Safety is conducting a pilot program that uses a structured multi-attribute drug product search engine in an effort to determine drug names that have a potential for confusion. These drug names are then listed and ranked based on frequency and severity of confusion. Ezetimibe and Zetia <sup>®</sup> results are listed below.

**Table 6: Look-Alike Sound-Alike Risk** <sup>13,14</sup>

Name	LASA Names	Severity	Frequency
Ezetimibe	Escitalopram oxalate 10mg, eszopiclone 1mg, glipizide 10mg	Mild	Occasional
Zetia <sup>®</sup>	Zebeta 10mg, Zovia 1/150, Zerit 1mg, Meridia 10mg, Zyrtec 10mg, Voltaren, Vysken	Mild	Occasional

**FDA Risk Evaluation and Mitigation Strategy (REMS):** <sup>17</sup>

None

**Drug Interactions:** <sup>7</sup>

Cyclosporine: Increased exposure to both ezetimibe and cyclosporine. Use caution and monitor cyclosporine concentrations.

Cholestyramine: Decreases the mean AUC by approximately 55%

Coumadin: Appropriate monitoring of INR should occur although not a significant interaction

Fibrates: Increase cholesterol excretion into the bile and can lead to cholelithiasis. Ezetimibe may also increase cholesterol in the bile and therefore the combination of ezetimibe with fibrates is not recommended.

**Conclusions:**

Ezetimibe is the first member of a 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 the CA IMT.

**Recommendations:**

Based on the available current evidence, no changes are recommended to be made to the IHS National Core Formulary.

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## **Authors:**

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