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# Ezetimibe

(Zetia<sup>®</sup> - Merck/Schering-Plough)

### Summary

**Indications:** Ezetimibe, alone or in combination with HMG-CoA reductase inhibitors (statins), is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B (Apo B) in patients with primary hypercholesterolemia. Ezetimibe, in combination with atorvastatin or simvastatin, is indicated for the reduction of TC and LDL-C in patients with homozygous familial hypercholesterolemia. Ezetimibe is also indicated as adjunctive therapy to diet for the reduction of sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

**Monitoring Parameters:** The most common adverse reactions are upper respiratory tract infections, headache, myalgia, arthralgia, and back pain. In controlled clinical combination studies of ezetimibe initiated concurrently with an HMG-CoA reductase inhibitor, the incidence of consecutive elevations ( $\geq$  3 times the upper limit of normal) in serum transaminases was 1.3% for patients treated with ezetimibe administered with HMG-CoA reductase inhibitors and 0.4% for patients treated with HMG-CoA reductase inhibitors alone. Patients with elevations in transaminases were generally asymptomatic; these elevations were not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment. When ezetimibe is co-administered with an HMG-CoA reductase inhibitor, liver function tests should be performed at initiation of therapy and according to the recommendations of the HMG-CoA reductase inhibitor.

**Dose:** The recommended dose is 10 mg orally once daily with or without food. Ezetimibe should be administered two hours before or 4 hours after bile acid sequestrants.

**Pregnancy Category:** C. There are no adequate or well-controlled studies of ezetimibe in pregnant women. Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the fetus. In animal studies done in rats, an increased incidence of skeletal abnormalities was seen at approximately 10 times the human exposure at 10 mg daily. Ezetimibe did cross into the placenta when rabbits and rats were exposed to multiple oral doses.

**Breast Feeding:** It is not known whether ezetimibe is excreted into human breast milk. In rat studies, exposure to total ezetimibe in nursing pups was up to half that observed in

maternal plasma. Ezetimibe should only be used in nursing mothers when the potential benefit justifies potential risk to the infant.

**Pediatrics:** In adolescents (aged 10 to 18 years), the pharmacokinetics of ezetimibe are similar to that seen in the adult population. Treatment experience in clinical trials in the pediatric population was limited to four patients with sitosterolemia and five patients with homozygous familial hypercholesterolemia. Treatment of children under the age of ten is not recommended.

**Geriatrics:** In the patients age 65 and over in clinical trials, there were no differences in safety and efficacy.

**Cost:** Ezetimibe is available in a 10 mg tablet. The average wholesale price (AWP) is \$2.41 per 10 mg tablet.

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### Introduction

Ezetimibe is the first FDA-approved medication in a new class of cholesterol-lowering agents that inhibit the intestinal absorption of cholesterol. Approximately 60% of the estimated 13 million patients taking HMG-CoA reductase inhibitors (statins) continue to have LDL-C levels higher than National Cholesterol Education Program (NCEP) recommended goals. Used alone or in combination with statins, ezetimibe offers a new medication option to get patients to achieve NCEP goals.

### Pharmacology/Pharmacokinetics

Ezetimibe selectively inhibits intestinal absorption of dietary and biliary cholesterol and plant sterols.<sup>2-5</sup> The precise mechanism of action is unknown but the theory is that ezetimibe inhibits cholesterol absorption at the brush border of the small intestine, resulting in decreased intestinal cholesterol delivered to the liver. This causes a reduction in hepatic cholesterol stores and an increase in cholesterol clearance from the circulation.

Ezetimibe has variable bioavailability. It is extensively metabolized in the small intestine and liver to ezetimibe-glucuronide, an active metabolite. The C<sub>max</sub> of ezetimibe and

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**Table 1. Drug Interactions**

Interacting Drug	Effect
Fibrates	Unknown; fibrates may increase cholesterol secretion into the bile, leading to cholelithiasis; concurrent use not recommended
Antacids	Decreased C <sub>max</sub> of ezetimibe but no effect on bioavailability or AUC
Cholestyramine	Decreased ezetimibe AUC; LDL reduction may be less; separate dose of ezetimibe to at least 2 hours before or 4 hours after cholestyramine
Gemfibrozil	Increased bioavailability of ezetimibe
Fenofibrate	Ezetimibe C <sub>max</sub> and AUC increased
Cyclosporine	Total ezetimibe concentration increased
Warfarin	No effect on warfarin bioavailability or prothrombin time

ezetimibe-glucuronide is 3.4 to 5.5 ng/ml and 45 to 71 ng/ml, respectively. The t<sub>max</sub> for ezetimibe and ezetimibe-glucuronide is 4 to 12 hours and 1 to 2 hours, respectively. Food does not affect the extent of absorption; however C<sub>max</sub> is increased approximately 38% when ezetimibe is taken with high fat food. Ezetimibe does not affect the plasma concentration of the fat-soluble vitamins.

The parent compound and the active metabolite are highly protein bound (> 90%). Both compounds have a half-life of about 22 hours and undergo enterohepatic recycling which repeatedly delivers the compounds back to the intestine, reducing systemic exposure. These two characteristics permit once daily dosing. Seventy-eight percent of the dose is excreted in the feces and 11% is renally eliminated. In patients with moderate or severe hepatic impairment, it has been observed that the mean area under the curve for ezetimibe was increased 3 to 4 fold and 5 to 6 fold, respectively. Due to the unknown effects of increased exposure to the drug, ezetimibe is not recommended in patients with moderate to severe hepatic insufficiency.

Ezetimibe has no significant effects on drugs metabolized by the cytochrome P450 system. Drug interactions described in the package insert are summarized in Table 1.<sup>1</sup>

## Clinical Trials

### Primary Hypercholesterolemia - Monotherapy

A phase III, multi-center, randomized, double-blinded, placebo controlled trial of 892 patients with primary hypercholesterolemia was conducted to determine the safety and efficacy of ezetimibe as monotherapy.<sup>6</sup> The study consisted of three phases: a 2-12 week screening/drug washout period; a 4-8 week single-blind placebo run in phase (during which baseline values were drawn); and a 12 week double-blind treatment phase. All subjects had a baseline LDL-C between 130-250 mg/dl and triglycerides ≤ 350 mg/ml. Patients were maintained on a NCEP Step 1 or stricter diet for at least two weeks (the NCEP Step 1 diet consists of < 30% of calories from total fat,

< 10% of calories from saturated fat, and < 300 mg/day of cholesterol). Patients were randomized to receive either ezetimibe 10 mg daily or placebo during the treatment phase.

Treatment with ezetimibe resulted in a mean reduction of LDL-C of 17% from baseline compared with an increase of 0.4% with placebo treatment (p<0.01). Sub-group analyses revealed that response to ezetimibe was consistent across all subgroups regardless of risk factor status, gender, age, race or baseline lipid profile. Patients treated with ezetimibe also demonstrated significantly decreased Apo B, TC, and triglycerides (TG) and significantly increased high density lipoprotein cholesterol (HDL-C) levels (p<0.01) compared to those treated with placebo.

A second similarly designed clinical trial conducted by Knopp et al confirmed these results.<sup>7</sup> Following stabilization on a NCEP Step 1 or stricter diet, a 2 to 12 week washout period and a 4 week, single-blind lead in period, 827 patients were randomized to receive either ezetimibe 10 mg or placebo. Subjects had baseline LDL-C levels between 130 and 250 mg/dl and triglycerides ≤ 350 mg/ml. After 12 weeks of therapy, the ezetimibe treated patients exhibited a 17.7% decrease in LDL-C compared to a 0.8% increase in the placebo group (p<0.01). A statistically significant decrease was seen in TC as was an increase in HDL in the ezetimibe treated patients vs. patients treated with placebo. Table 2 summarizes the results of the monotherapy clinical trials.

### Primary Hypercholesterolemia - Combination Therapy

The safety and efficacy of adding ezetimibe to ongoing statin therapy in 769 patients with primary hypercholesterolemia was evaluated in a randomized, double blind, placebo controlled study (Add-On Study).<sup>10</sup> Enrolled patients had not achieved LDL-C goal for their risk category on a stable dose of a statin (≥ 6 weeks of therapy). Patients were randomized to receive ezetimibe 10 mg daily or placebo in addition to their statin therapy for eight weeks. The statin dose remained constant for the study period.

**Table 2. Clinical Efficacy: Ezetimibe Monotherapy**

Monotherapy Studies				
Study/Design	Population	Treatment	Results	Comments
MC, R, DB, PC <sup>6</sup> 12 weeks	N = 892 Primary hypercholesterolemia LDL: 130 – 250 mg/dL TG: ≤ 350 mg/dL	EZE 10 mg QAM Placebo	<b>LDL:</b> -16.9% vs 0.4% (p<0.01) <b>TG:</b> -5.7% vs 5.7% (p<0.01) <b>HDL:</b> 1.3% vs -1.6% (p<0.01)	Data not presented but noted in the study that results were consistent regardless of baseline lipid profile
R, DB, PC, PG <sup>7</sup> 12 weeks	N = 827 Primary hypercholesterolemia LDL: 130 – 250 mg/dL TG: ≤ 350 mg/dL	EZE 10 mg QAM Placebo	<b>LDL:</b> -17.7% ± 0.6 vs 0.8% ± 0.9 (p < 0.01) <b>HDL:</b> 1% ± 0.5 vs -0.8% ± 1.3 (p < 0.01) <b>TC:</b> -12.4% ± 0.4 vs 0.6% ± 0.6 (p < 0.01) <b>TG:</b> -1.7% ± 1.4 vs 2.4% ± 2.2 (NS)	
Phase II dose range study <sup>8</sup> 8 weeks	N = 124 LDL: 130 – 250 mg/dL TG: ≤ 300 mg/dL	EZE 1 mg EZE 5 mg EZE 10 mg EZE 20 mg EZE 40 mg LOV 40 mg Placebo	-14.6%* -15.7%* -16.4%* -17.9%* -20%* -31.8%* 3.8 * p < 0.05 vs placebo	
Pooled analysis of two Phase II studies <sup>9</sup> MC, PC, DB, R, PG 12 weeks	N = 432 Primary hypercholesterolemia LDL: 130 – 250 mg/dL TG: ≤ 300 mg/dL	EZE 0.25 mg EZE 1 mg EZE 5 mg EZE 10 mg Placebo	5 mg: - 15.7% (p < 0.01 vs placebo) 10 mg: 18.5% (p < 0.01 vs placebo; p < 0.05 vs 5 mg)	
		EZE 5mg AM EZE 5 mg PM EZE 10 mg AM EZE 10 mg PM Placebo	Timing of dose had no effect on results	

MC = multi-center; PC = placebo-controlled; DB = double-blind; R = randomized; PG = parallel group; EZE=ezetimibe

Addition of ezetimibe to the ongoing statin therapy provided an additional 25% reduction in LDL-C versus 4% in patients receiving placebo plus a statin (p<0.0001). This reduction was consistent among all statin subgroups. In addition, a 14% reduction in TG was seen in the ezetimibe + statin treated group compared to a 2.9% reduction in the placebo + statin treated group (p<0.001). NCEP ATP II target LDL-C goal was achieved by 75.5% of patients treated with statin plus ezetimibe versus 27% of the statin plus placebo group (p<0.01).

Randomized, placebo-controlled studies looking at co-administration of ezetimibe with atorvastatin, simvastatin, pravastatin and lovastatin have been conducted.<sup>11-14</sup> The design of each of the studies was similar featuring three phases: a 6-16 week screening phase (drug washout and diet stabilization), a 6 week pre-randomization phase (single blind placebo run-in, completion of drug washout, and baseline blood samples obtained), and a 8 to 12 week randomized, active treatment

phase. All patients were on NCEP Step 1 or stricter diet. The primary efficacy endpoint was the mean percent reduction in LDL-C from baseline. Secondary efficacy endpoints included TC, HDL-C, other coronary heart disease (CHD) markers and percent of patients that reached ATP III goal or at least a 15% LDL-C reduction. The results of the four studies are summarized in the Table 3. The studies demonstrated an additional mean LDL-C reduction of 12 to 14% when comparing the ezetimibe plus statin groups to the statin only treated groups.

#### *Homozygous Familial Hypercholesterolemia*

A multi-center, double-blind randomized controlled trial conducted by Gagne et al included fifty patients with homozygous familial hypercholesterolemia.<sup>15</sup> The patients were on a NCEP Step 1 or stricter diet. The study consisted of two treatment phases - the first was a 6 to 14 week open label non-randomized treatment with a statin, when patients were taking either simvastatin 40 mg per day or atorvastatin 40 mg per day.

**Table 3. Clinical Efficacy: Ezetimibe/Statin Combination Therapy**

Combination Therapy Studies				
Study/Design	Population	Treatment	Results	Comments
MC, R, DB, PC <sup>11</sup> 12 weeks	N = 668 Primary hypercholesterolemia LDL: 145-250 mg/dL TG: ≤ 350 mg/dL	EZE 10mg SIM 10mg EZE 10mg/SIM 10mg SIM 20 mg EZE 10mg/SIM 20mg SIM 40mg EZE 10mg/SIM 40mg SIM 80 mg EZE 10/SIM 80 Placebo	<u>EZE/SIM (pooled doses)</u> LDL: -49.9% (p < 0.01 vs SIM alone and EZE alone) <u>SIM alone (pooled doses)</u> LDL: -36.1% <u>EZE alone</u> LDL: -18.1% <u>Placebo:</u> LDL: -1.3% Incremental mean % change statistically significant	ATP III levels reached in 77% in EZE/SIM pts vs 64% SIM alone.
MC, R, DB, PC <sup>12</sup> 12 weeks	N = 628 Primary hypercholesterolemia LDL: 145-250 mg/dL TG: ≤ 350 mg/dL	EZE 10 mg ATOR 10 mg ATOR 20 mg ATOR 40 mg ATOR 80 mg EZE 10 mg/ATOR 10 EZE 10 mg/ATOR 20 EZE 10 mg/ATOR 40 EZE 10 mg/ATOR 80 Placebo	<u>EZE/ATOR (pooled doses):</u> LDL: -54.5% (p < 0.01 vs ATOR alone) <u>ATOR alone (pooled doses):</u> LDL: -42.4% <u>EZE alone:</u> LDL: -18.4% <u>Placebo:</u> LDL: 5.9%	HDL and triglycerides also positively affected with ezetimibe  LDL reduction with EZE/ATOR 10 ~ ATOR 80 (-50% vs - 51%)
R, DB, PC <sup>13</sup> 12 weeks	N = 538 Primary hypercholesterolemia LDL: 145-250 mg/dL TG: ≤ 350 mg/dL	EZE 10 mg PRV 10 mg PRV 20 mg PRV 40 mg EZE 10 mg/PRV 10 mg EZE 10 mg/PRV 20 mg EZE 10 mg/PRV 40 mg Placebo	<u>EZE/PRV (pooled doses):</u> LDL: -37.7% (p < 0.01 vs. PRV alone) <u>PRV alone (pooled doses):</u> LDL: -24.3% <u>EZE alone:</u> LDL: - 18.7% <u>Placebo:</u> LDL: 1.3%	
MC, R, DB, PC <sup>14</sup> 12 weeks	N = 548 Primary hypercholesterolemia LDL: 145-250 mg/dL TG: ≤ 350 mg/dL	EZE 10 mg LOV 10 mg LOV 20 mg LOV 40 mg EZE 10 mg/LOV 10 EZE 10 mg/LOV 20 EZE 10 mg/LOV 40 Placebo	<u>EZE/LOV (pooled doses):</u> LDL: -39% (p < 0.01 vs. LOV alone) <u>LOV (pooled doses):</u> LDL: -24.7% <u>EZE alone:</u> LDL: - 18.6% <u>Placebo:</u> LDL: -0.03%	

MC = multi-center; PC = placebo-controlled; DB = double-blind; R = randomized; EZE = ezetimibe; SIM = simvastatin; ATOR = atorvastatin; PRV = pravastatin; LOV = lovastatin

In the second phase of the study, patients were randomized to one of three double-blind treatments: statin 80 mg daily; ezetimibe 10 mg plus statin 40 mg daily; or ezetimibe 10 mg plus statin 80 mg daily. Patients received the same statin in the second phase of the study as they took during the open label phase, though dose and addition of ezetimibe or placebo was blinded.

Ezetimibe plus statin 40 mg or 80 mg dose significantly reduced LDL-C levels compared to 80 mg statin dose alone (-20.7% vs. 6.7%, p=0.007). Ezetimibe plus statin 80 mg reduced LDL-C by an additional 20.5% (p=0.0001) versus statin 80 mg plus placebo.

### Adverse effects

Ezetimibe was well tolerated in clinical trials, with an adverse effect profile similar to either placebo in placebo-controlled studies or statin monotherapy in combination studies. Adverse reactions reported in more than two percent of patients and occurring more often in ezetimibe patients than placebo are outlined in Table 4 for monotherapy studies and Table 5 for combination therapy studies. The most common reactions were upper respiratory tract infections, headache, myalgia, arthralgia, and back pain.

The incidence of increased liver function tests was similar between ezetimibe and placebo. When ezetimibe was combined with statins, the incidence of increased liver function

**Table 4. Adverse Events in at Least 2% of Patients, at an Incidence Greater Than Placebo (Monotherapy studies)**

Adverse Event	Placebo (%) n = 795	Ezetimibe 10 mg (%) n = 1691
Back pain	3.9	4.1
Arthralgia	3.4	3.8
Diarrhea	3.0	3.7
Sinusitis	2.8	3.6
Abdominal pain	2.8	3.0
Pharyngitis	2.1	2.3
Coughing	2.1	2.3
Fatigue	1.8	2.2
Viral infection	1.8	2.2

tests was higher in the combination group than in the statin only group, but the patients were generally asymptomatic. There was no excess of myopathy or rhabdomyolysis.

#### Cost, dose, how supplied

Ezetimibe is available as a 10 mg capsule-shaped tablet, at a cost of \$72.30 per month (based on AWP price). The recommended dose is 10 mg daily taken with or without food. When taken in combination with a statin, ezetimibe can be administered at the same time of day as the statin, according to the dosing recommendation of the statin. Ezetimibe should be

administered two hours before or 4 hours after bile acid sequestrants.

Ezetimibe should be avoided in those patients allergic to any of its ingredients. When taken in combination with a statin, ezetimibe should be avoided by patients with active liver disease or unexplained persistent elevations of liver enzymes.

#### Conclusions

Ezetimibe is the first drug in a new class of lipid lowering medications that has a different mechanism than other currently available medications. It is believed that ezetimibe inhibits intestinal absorption of cholesterol in the small intestine. Ezetimibe has few drug interactions and is well tolerated with an adverse event profile comparable to placebo or statins alone, if ezetimibe is combined with a statin.

Ezetimibe alone reduces LDL-C 17 to 18%. When ezetimibe is combined with a statin, the LDL-C reduction from baseline is approximately 50%, compared to a 35 to 40% reduction in the combined group of all doses of statin-only. Ezetimibe added to a stable dose of a statin reduced LDL-C 25% compared to a 4% reduction with the statin alone, for an additional 21% reduction. In the phase I/II dose range finding studies, LDL reduction with doses higher than 10 mg was not significantly different than the 10 mg dose.

Statins are still considered first line therapy for patients requiring LDL-C reduction. For patients with contraindications to, or drug interactions with the statins, ezetimibe is a reasonable first line agent. Ezetimibe will likely be used in combination with statins or for those patients unable to tolerate the statins. ■

*References available upon request*

**Table 5. Adverse Events in Greater Than 2% of Patients, at an Incidence Greater Than Placebo (Combo therapy studies)**

Adverse Event	Placebo (%) n=259	Ezetimibe(%) n=262	All Statin (%) n=936	Ezetimibe/All Statins (%) n=925
Upper resp. tract infection	10.8	13	13.6	11.8
Headache	5.4	8	7.3	6.3
Myalgia	4.6	5	4.1	4.5
Back pain	3.5	3.4	3.7	4.3
Sinusitis	1.9	4.6	3.6	3.5
Abdominal pain	2.3	2.7	3.1	3.5
Arthralgia	2.3	3.8	4.3	3.4
Diarrhea	1.5	3.4	2.9	2.8
Fatigue	1.9	1.9	1.4	2.8
Pharyngitis	1.9	3.1	2.5	2.3
Chest pain	1.2	3.4	2	1.8
Dizziness	1.2	2.7	1.4	1.8

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