National PBM Drug Monograph
EZETIMIBE (ZETIA®)
June 2005
VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary

Efficacy:

There have been numerous studies evaluating the effect of ezetimibe combined with statins on lipid levels. The addition of ezetimibe 10 mg daily to statin therapy generally results in an additional 12-15% reduction in LDL-C (up to 20%), 7-13% reduction in triglycerides and an increase in HDL-C of 1-5%. In all of the published clinical trials, maximum LDL-C lowering ability of ezetimibe was observed at 2 weeks. In many of these trials, significantly more patients had LDL-C reductions in excess of 50% compared to the statin alone. In addition, more patients met their LDL-C goals on combination therapy versus those on statins alone.

To date, there have been no published clinical outcome or atherosclerotic progression trials examining the cardiovascular benefit of the ezetimibe either alone or in combination with statins. However, there are two trials that are underway that will help to determine the incremental benefit of adding ezetimibe to statins. The IMPROVE-IT trial is a clinical endpoint trial comparing the combination of ezetimibe plus simvastatin versus simvastatin alone. The ENHANCE trials is an atherosclerotic progression trial comparing the combination of ezetimibe plus simvastatin to simvastatin alone. These trials are planned to follow patients for 2 years.

Ezetimibe combined with a low dose statin can produce similar LDL-C lowering as quadruple the statin dose (e.g. simva 10 mg + ezetimibe 10 mg = simva 80 mg daily). Similarly, addition of niacin or bile acid sequestrants (BAS) to low dose statins can result in a reduction in LDL-C similar to maximum dose statins. However, since most of the large health outcome statin trials utilized higher statin doses, it is not known whether the same clinical benefit will be seen if a low dose statin is combined with ezetimibe or another agent.

Safety:

Liver enzymes

Monotherapy: In clinical trials, comparing ezetimibe to placebo, clinically significant elevation in liver function tests (LFTs) (≥3X upper limit of normal) were not significantly different between groups (0.5% vs. 0.3%, respectively)

In combination with statins: In clinical trials comparing ezetimibe in combination with statins versus statins alone, clinically significant elevation in LFTs occurred in 1.3% of patients receiving combination therapy vs. 0.4% in those receiving statins alone.

In March 2004, Merck submitted safety and efficacy data from several unpublished extension studies with ezetimibe in combination with statins. In one of these long-term studies, clinically important elevation in LFTs occurred in 2.8% receiving combination therapy vs. 0.4% on statin monotherapy. Several clinical trials comparing combination therapy of ezetimibe with statins compared to statins alone did show a numerically higher incidence of LFT elevation in the combination group (refer to appendix A for details). The elevations were typically asymptomatic, not associated with cholestasis and returned to baseline upon discontinuation of treatment or continued treatment.

Ezetimibe is not recommended in patients with moderate or severe liver impairment because the effect of increased exposure to ezetimibe is unknown in these patients.

Muscle toxicity

Monotherapy: In clinical trials, there was no difference in myotoxicity between ezetimibe and placebo.

In combination with statins: In clinical trials combining ezetimibe with a statin vs. statins alone, there was no increased risk for myopathy with ezetimibe.

Recently, a letter was published in the Annals of Internal Medicine reporting two cases of suspected myopathy occurring soon after the addition of ezetimibe (Fux, Ann Intern Med 2004). One of those patients was receiving atorvastatin 80 mg and the other fluvastatin 80 mg. A response to this letter (Phillips, Ann Intern Med 2004) stated that they had observed a similar experience.

Drug Interactions

- Based upon a "cocktail" study in twelve healthy adult males using probe drugs (caffeine, dextromethorphan, tolbutamide, and IV midazolam), known to be metabolized by cytochrome P450 enzymes (1A2, 2D6, 2C8/9 and 3A4), ezetimibe did not inhibit or induce metabolism of cytochrome P450 isoezymes.
- The manufacturer reports no significant drug interactions with warfarin, digoxin, statins, oral contraceptives, cimetidine, antacids and glipizide,
- The area under the curve (AUC) for ezetimibe was increased 1.7 fold with gemfibrozil and 1.5 fold with fenofibrate. (see precaution section for reasons not to combine ezetimibe with fibrates).
- Concomitant administration of ezetimibe with cholestyramine resulted in a 55% reduction in ezetimibe's AUC which may result in a lower than expected LDL-C reduction.
- In one patient taking multiple medications, including cyclosporine, ezetimibe concentrations were increased 12-fold. The manufacturer recommends close monitoring when combining cyclosporine with ezetimibe.
- Fibrates work by increasing cholesterol excretion into the bile which can lead to cholelithiasis. In an animal study, ezetimibe increased cholesterol in the gallbladder bile. Combination of ezetimibe with fibrates is not recommended until human studies are completed.

Dosing

The dose of ezetimibe for all indications is 10 mg daily whether prescribed as monotherapy or in combination with a statin. There is limited information on the LDL-C lowering response of ezetimibe 5 mg daily. (See full monograph for details)

Laboratory Monitoring

When ezetimibe is administered in combination with a statin, liver function tests (LFTs) should be performed prior to initiation of therapy and according to the recommendations of the statin (e.g. simvastatin: semiannually for the first year or until one year after the last increase in dose).

Recommendations:

Ezetimibe to remain nonformulary at National and VISN levels with alterations in current criteria for use:

Combination therapy

In patients not achieving their LDL-C goals with high-dose statins (maximum doses) or the highest recommended or tolerated statin dose, clinicians are advised to consider add-on therapy with niacin. In HATS (HATS-Brown 2001), the combination of statins plus niacin led to regression of atherosclerosis and a relative reduction in clinical events of 90% versus placebo. However, there are some patients that may not be candidates for niacin including those with a history of documented peptic ulcer disease, gouty attacks and/or poorly controlled diabetes. In those patients not reaching their LDL-C goals with add-on niacin; unable to tolerate niacin; or are not candidates for niacin, addition of either a BAS or ezetimibe (nonformulary) to statins can be considered.

Monotherapy

Ezetimibe should not be considered first line for patients with elevated LDL-C who cannot tolerate statins since there are other lipid-lowering therapies (niacin or BAS) with clinical trial evidence to support reductions in CHD outcomes. However, ezetimibe may be considered as monotherapy in patients unable to tolerate statins and having an inadequate LDL-C lowering response, intolerance or contraindication to niacin and BAS.

Due to the potential variability in response to cholesterol absorption inhibitors, and since the maximum LDL-C response from ezetimibe can be seen as early as the first 2 weeks, assessment of response should be made within the first month of therapy. Monitoring of LFTs is recommended with the ezetimibe-statin combination.

Introduction

The third expert report of the National Cholesterol Education Program (NCEP) recognizes low-density lipoprotein cholesterol (LDL-C) to be the primary target in the management of hypercholesterolemia. As a result, recommendations for initiation of treatment and for goals of therapy are based primarily upon LDL-C.[1] Although controversial, some experts are recommending more aggressive LDL-C goals for very high risk patients including those experiencing acute coronary syndrome (ACS)[2] and more recently, for secondary prevention.[3] It has been estimated that less than 40% of patients reach their target LDL-C goals on lipid lowering therapies and even more striking, only about 18% of high-risk patients achieve their LDL-C goals.[4] There may be several reasons for failure to meet LDL-C goals including initiation of low doses of lipid-lowering medications, inadequate or lack of statin titration, nonadherence to drug therapy and difficult to achieve LDL-C goals.

This document is an update and will focus primarily on combination therapy of ezetimibe with statins. The review will be used to determine whether changes in formulary status or criteria for use for ezetimibe are indicated. Ezetimibe (Zetia®) is the first in a new class of cholesterol lowering agents called the cholesterol absorption inhibitors.

Pharmacology/Pharmacokinetics[5]

Ezetimibe acts by selectively inhibiting absorption of cholesterol (dietary and biliary) at the brush border of the small intestine. This reduction in cholesterol absorption leads to a decrease in the amount of intestinal cholesterol presented to the liver. As a result, there is a compensatory increase in the production of cholesterol in the liver. However, the net result is a reduction in low-density lipoprotein cholesterol (LDL-C) of approximately 18% compared to 1% with placebo.

Table 1.

Pharmacokinetic Parameter	
Absorption	▪ Mean peak plasma concentrations of ezetimibe are reached within 4-12 hours and ezetimibe-glucuronide within 1-2 hours. ▪ The absolute bioavailability cannot be determined because the compound is virtually insoluble in aqueous media suitable for injection. ▪ Food has no effect on the extent of absorption so ezetimibe can be taken without regard to meals.
Distribution	▪ Ezetimibe and ezetimibe-glucuronide are highly bound to plasma proteins (>90%)
Metabolism	▪ Ezetimibe is conjugated to an active metabolite ezetimibe-glucuronide accounting for 80-90% of total drug in plasma. Ezetimibe is also active accounting for 10-20% of total drug in plasma. ▪ Plasma-concentration time profiles exhibit multiple peaks suggesting enterohepatic recycling.
Excretion	▪ Half-life of ezetimibe and ezetimibe-glucuronide is approximately 22 hours ▪ Approximately 78 % is excreted in feces and 11% in urine. (ezetimibe was the major component in feces and ezetimibe-glucuronide was the major component in urine)

FDA Approved Indications and Off-label Uses[5]

- Ezetimibe is indicated, as an adjunct to diet, as monotherapy or in combination with statins in patients with primary hypercholesterolemia (heterozygous and familial and non-familial) to reduce total cholesterol, LDL-C, and apolipoprotein B.

- Ezetimibe is indicated for homozygous familial hypercholesterolemia in combination with simvastatin or atorvastatin as an adjunct to other lipid lowering treatments (e.g. LDL apheresis) for the reduction of total cholesterol and LDL-C.

- Ezetimibe is indicated, as an adjunct to diet, in those patients with homozygous sitosterolemia for the reduction of elevated sitosterol and campesterol levels.

Current VA National Formulary Status

Ezetimibe is not on the VA National Formulary or VISN formularies but is available on a nonformulary basis. Nonformulary criteria for using ezetimibe can be found at http://www.pbm.va.gov or http://vaww.pbm.va.gov

Dosage and Administration

The dose of ezetimibe for all indications is 10 mg daily whether prescribed as monotherapy or in combination with a statin. However, some advocate using a 5 mg dose. In a pooled analysis of two phase II studies, the LDL-C lowering response of 0.25 mg, 1 mg, 5 mg and 10 mg of ezetimibe (monotherapy) was examined in 432 patients for 12 weeks. The 5 mg dose reduced LDL-C by 15.7% and the 10 mg by 18.5% ($P<0.05$ in favor of 10 mg dose). In the 5 mg group, 54% of patients had a reduction in their LDL-C of $\geq$15% and 67.8% of those in the 10 mg group had reductions in their LDL-C of $\geq$15%.[35] In another study, a small number of patients (n=8 in each group) were randomized to lovastatin 20 mg, lovastatin 20 mg + ezetimibe 5 mg, lovastatin 20 mg + ezetimibe 10 mg, lovastatin 20 mg + ezetimibe 20 mg or lovastatin 40 mg + ezetimibe 10 mg for 2 weeks. Addition of ezetimibe resulted in an additional reduction in LDL-C of 16-18% compared to lovastatin alone. There were no differences in LDL-C lowering response observed between 5, 10 or 20 mg of ezetimibe.[36]

Efficacy Measures

The third expert report of the National Cholesterol Education Program (NCEP) recognizes low-density lipoprotein cholesterol (LDL-C) to be the primary target in the management of hypercholesterolemia. As a result, most clinical trials involving newer lipid-lowering therapies use LDL-C as a surrogate endpoint. However, trials evaluating clinical outcomes are the gold standard for measuring benefit of lipid-lowering therapies.

Ezetimibe: Summary of Efficacy Findings

There have been numerous studies evaluating the effect of ezetimibe combined with statins on lipid levels. The addition of ezetimibe to statin therapy generally results in an additional 12-15% reduction in LDL-C (up to 20%), 7-13% reduction in triglycerides and an increase in HDL-C of 1-5%. In all of the published clinical trials, maximum LDL-C lowering ability of ezetimibe was observed at 2 weeks. (Refer to appendix A for further details from clinical trials of LDL-C lowering of ezetimibe in combination with statins). In many of these trials, significantly more patients had LDL-C reductions in excess of 50% compared to the statin alone. In addition, more patients met their LDL-C goals on combination therapy versus those on statins alone.

To date, there have been no published clinical outcome or atherosclerotic progression trials examining the cardiovascular benefit of the ezetimibe either alone or in combination with statins. However, the IMPROVE-IT trial was announced in November 2004. The Improved Reduction of Outcomes: VYTORIN (ezetimibe 10/simvastatin 40) Efficacy International Trial or IMPROVE-IT will evaluate, over a 2-year

period, the combination of ezetimibe plus simvastatin versus simvastatin 40 mg alone in 10,000 recent ACS patients. The primary endpoint is the composite of death, MI, rehospitalization for ACS or revascularization. In February 2005, the design and rationale for Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regressions (ENHANCE) trial was published. In ENHANCE, the combination of ezetimibe plus simvastatin (10/80) will be compared to simvastatin 80 mg to determine if there are greater benefits with combination therapy with regard to reducing carotid artery intima-media thickness. This trial will follow patients for 2 years.[32]

Ezetimibe combined with a low dose statin can produce similar LDL-C lowering as quadruple the statin dose (e.g. simva 10 mg + ezetimibe 10 mg = simva 80 mg daily). However, since most of the large health outcome statin trials utilized higher statin doses, it is not known whether the same clinical benefit will be seen if a low dose statin is combined with ezetimibe or another agent.

Other Potential "Add-On" Therapeutic Options For Hypercholesterolemia

Bile acid sequestrants (BAS) have the ability to reduce LDL-C by approximately 15-27% (colestipol 5-15 g/d) and slightly raise HDL-C. The major limitations of BAS are their tolerability (GI adverse effects), potential for drug interactions (if taken at the same as other medications) and they can increase triglyceride concentrations.[8-9] In the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) patients receiving cholestyramine for 7.4 years experienced a reduced rate of CHD death and nonfatal MI (RRR 19%, ARR 1.6%, $p<0.05$, NNT 62), but no overall mortality benefit compared to placebo/diet.[10]

Niacin has the ability to reduce LDL-C by approximately 15-20%(1-2 g/d), triglycerides by 20-35%(1 g/d) and raise HDL-C by 15-30% (1 g/d). The primary limitation of niacin are the flushing side effects which can occur with both immediate and sustained release products but can be minimized by giving low dose aspirin 30 minutes prior to niacin. Higher doses of niacin may raise glucose or uric acid concentrations and should be avoided in patients with a history of gout or peptic ulcer disease. Two recent trials demonstrated the safety and efficacy of an extended release niacin product (Niaspan 1000-3000mg/d) in diabetics managed by diet, oral hypoglycemics, or insulin.[11-12] Although hemoglobin A1C was statistically increased at higher niacin doses, the changes may not be considered clinically significant. Serious liver toxicity has been reported in patients receiving sustained release niacin in doses of >2 grams daily.[8-9] In the Coronary Drug Project, men with known coronary artery disease (CAD), receiving niacin for 5 years, had a significant reduction in nonfatal MI (RRR 27%, ARR 3.6%, NNT 28) and all stroke (RRR 24%, ARR 2.7%, NNT 37), but no benefit in overall mortality.[13]

Similar to ezetimibe, adding a BAS or niacin to low dose statin therapy typically results in a LDL-C reduction similar to that seen with quadruple the statin dose (e.g. simva 10 mg + ezetimibe 10 mg = simva 80 mg daily). However, to restate, since most of the large health outcome statin trials utilized higher statin doses, it is not known whether the same clinical benefit will be seen if a low dose statin is combined a BAS or niacin.

In the third report from the Adult Treatment Panel (ATP III) or NCEP, bile acid sequestrants (BAS) or niacin are recommended in combination with statins for those not reaching their NCEP LDL-C targets with a statin alone. However to date, there have been no large, published clinical endpoint trials evaluating the benefits of combination pharmacologic therapies for dyslipidemia. There are, however, angiographic and LDL-C lowering trials demonstrating benefit with certain drug combinations (statins with BAS and statins with niacin). It should be emphasized that the available clinical trials, evaluating certain lipid-lowering combinations, do not necessarily represent the manner in which these combinations are used (e.g. Add-on after failure to meet LDL-C goals).

Table 2. Summary of Statin-Combination Results [1,14-20]

Drug Combination	Expected Change in Lipoproteins (%)			Angiographic Results	Considerations
	LDL (↓)	HDL (↑)	TG (↓)		
Additive Effects for reducing LDL-C when mono-therapy is inadequate					
1. Statin + BAS or resins	30-60	--	↑10	(Brown 1990) Lova 40 mg + colestipol 10 g three times daily: Less progression and more regression than placebo	Drug-drug interaction (take other drugs 1 hr before or 4-6 hrs after resin).
2. Statin + Niacin	25-57	13-36	19-38	(HATS 2001)-less progression and 90% less clinical events vs. placebo (p=0.03), (Arbiter-2 2004) (NS), (Hecht 2005)-(NS)	Risk of LFT abnormalities, especially with sustained release niacin products ≥2 g/day. Avoid niacin in patients with history of gout or peptic ulcer disease.
3. Statin + Ezetimibe	34-60	3-9	11-24	None (Design and Rationale of ENHANCE has been published)	IMPROVE-IT ezetimibe10 + simva 40 vs. simva 40 in 10,000 ACS patients announced November 2004.

Refer to Appendix B for details on clinical trials involving niacin

Adverse Effects [5]

Table 3.

Adverse Event	Placebo (%) (n=259)	Ezetimibe (%) (n=262)	All Statins (%) (n=936)	Ezetimibe + All Statins (%) (n=925)
Chest pain	1.2	3.4	2	1.8
Dizziness	1.2	2.7	1.4	1.8
Fatigue	1.9	1.9	1.4	2.8
Abdominal pain	2.3	2.7	3.1	3.5
Diarrhea	1.5	3.4	2.9	2.8
Arthralgia	2.3	3.8	4.3	3.4
Back pain	3.5	3.4	3.7	4.3
Myalgia	4.6	5	4.1	4.5

*Table adapted from Zetia Product Information. Adverse events, reported from combined ezetimibe/statin clinical trials, occurring in ≥2% of patients and at an incidence greater than placebo, regardless of causality.

Precautions [5]

Liver enzymes

Monotherapy: In clinical trials, comparing ezetimibe to placebo, clinically significant elevation in liver function tests (LFTs) (≥3X upper limit of normal) were not significantly different between groups (0.5% vs. 0.3%, respectively)

In combination with statins: In clinical trials comparing ezetimibe in combination with statins versus statins alone, clinically significant elevation in LFTs occurred in 1.3% of patients receiving combination therapy vs. 0.4% in those receiving statins alone.

In March 2004, Merck submitted safety and efficacy data from several unpublished extension studies with ezetmibe in combination with statins. In one of these long-term studies, clinically important elevation in LFTs occurred in 2.8% receiving combination therapy vs. 0.4% on statin monotherapy. Several clinical trials comparing combination therapy of ezetimibe with statins compared to statins alone did show a numerically higher incidence of LFT elevation in the combination group (refer to appendix A for details). The elevations were typically asymptomatic, not associated with cholestasis and returned to baseline upon discontinuation of treatment or continued treatment.

Ezetimibe is not recommended in patients with moderate or severe liver impairment because the effect of increased exposure to ezetimibe is unknown in these patients.

Muscle toxicity
Monotherapy: In clinical trials, there was no difference in myotoxicity between ezetimibe and placebo.
In combination with statins: In clinical trials combining ezetimibe with a statin vs. statins alone, there was no increased risk for myopathy with ezetimibe.

Recently, a letter was published in the Annals of Internal Medicine reporting two cases of suspected myopathy occurring soon after the addition of ezetimibe (Fux, Ann Intern Med 2004).[6] One of those patients was receiving atorvastatin 80 mg and the other fluvastatin 80 mg. A response to this letter (Phillips, Ann Intern Med 2004) stated that they had observed a similar experience.[7] Furthermore, they report evaluating 300 patients in their system with intolerance to lipid-lowering therapies. They describe a group of patients with common features suggesting impaired fatty acid oxidation as a possible mechanism for an increased susceptibility to myopathic symptoms. Thirty of these patients were given ezetimibe mono-therapy and 18 experienced a recurrence of their myopathic symptoms. Many patients in this group could not tolerate statins, niacin or fibrates. The authors of this letter suggest further study of impaired fatty acid oxidation as a possible mechanism for statin-associated myotoxicity.

In combination with fibrates (not recommended) [5]
Fibrates work by increasing cholesterol excretion into the bile, which can lead to cholelithiasis. In an animal study, ezetimibe increased cholesterol in the gallbladder bile. The manufacturer does not recommend combination of ezetimibe with fibrates until human studies are completed. In a recently published study, 625 patients with no known coronary artery disease were randomized to receive placebo, fenofibrate 160 mg, ezetimibe 10 mg or the combination for 12 weeks. The combination lowered LDL-C more than either agent alone. A shift towards a larger and more buoyant (less atherogenic) LDL-C particle was observed in a greater proportion of patients receiving fenofibrate or the combination compared to the ezetimibe or placebo groups. One case of cholecystitis and cholelithiasis with subsequent cholecystectomy was reported in the combination group. However, the investigator did not feel it was related to treatment. [37]

Monitoring [5]

When ezetimibe is administered in combination with a statin, LFTs should be performed prior to initiation of therapy and according to the manufacturer recommendations of the statin (e.g. simvastatin: semiannually for the first year or until one year after the last increase in dose).

Contraindications [5]

- Hypersensitivity to any component of ezetimibe.
- The combination of ezetimibe and a statin is contraindicated in any patient with active liver disease or unexplained persistent elevations in serum transaminases.

Look-alike / Sound-alike (LA/SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name <ezetimibe>: escitalopram oxalate 10 mg, eszopiclone 1 mg, glipizide 10 mg
Frequency: Occasional
Severity: Mild

LA/SA for trade name <Zetia or Vytorin>: Zebeta 10 mg, Zovia 1/150, Zerit 1 mg, Meridia 10 mg, Zyrtec 10 mg, Voltaren, Vantin, Vysken.
Frequency: Occasional
Severity: Mild

Drug Interactions [5]

- Based upon a "cocktail" study in twelve healthy adult males using probe drugs (caffeine, dextromethorphan, tolbutamide, and IV midazolam), known to be metabolized by cytochrome P450 enzymes (1A2, 2D6, 2C8/9 and 3A4), ezetimibe did not inhibit or induce metabolism of cytochrome P450 isoezymes.
- The manufacturer reports no significant drug interactions with warfarin, digoxin, statins, oral contraceptives, cimetidine, antacids and glipizide,
- The area under the curve (AUC) for ezetimibe was increased 1.7 fold with gemfibrozil and 1.5 fold with fenofibrate. (see precaution section for reasons not to combine ezetimibe with fibrates).
- Concomitant administration of ezetimibe with cholestyramine resulted in a 55% reduction in ezetimibe's AUC which may result in a lower than expected LDL-C reduction.
- In one patient taking multiple medications, including cyclosporine, ezetimibe concentrations were increased 12-fold. The manufacturer recommends close monitoring when combining cyclosporine with ezetimibe.
- Fibrates work by increasing cholesterol excretion into the bile which can lead to cholelithiasis. In an animal study, ezetimibe increased cholesterol in the gallbladder bile. Combination of ezetimibe with fibrates is not recommended until human studies are completed.

VA Contract and FSS Pricing

Table 4.

Drug and Dose/day	Cost/day ($)	Cost/Month ($)
Simvastatin		
10 mg	0.27	8.10
20 mg	0.47	14.10
40 mg	0.70	21.00
80 mg	0.94	28.20
Lovastatin		
20 mg	0.26	7.80
40 mg	0.26	7.80
80 mg	0.52	15.60
Atorvastatin		
10 mg	1.38	41.40
20 mg	1.86	55.80
40 mg	2.20	66.00
80 mg	2.06	61.80
Rosuvastatin		
5 mg/10 mg/20 mg/40 mg	1.52/1.43/1.45/1.52	45.60/42.90/43.50/45.60
BAS		
Colestipol * 10-15 gm Colestipol Tabs 2-4 gm Cholestyramine 4-8 gm	1.34-2.01 (Bulk) 1.94-2.91 (packets) 0.64-1.28 (initial dose) 0.16-0.32 (bulk-Sandoz) 0.54-1.08 (packets-Teva)	40.20-60.30 58.20-87.30 19.20-38.40 4.80-9.60 16.20-32.40
Niaspan+		
1-2 gm	0.42-0.84	12.60-25.20
Ezetimibe		
10 mg	1.43	42.90
Simva 10 + Eze 10	1.70	51.00
Simva 40 + Eze 10	2.13	63.90
Simva 80 + Eze 10	2.37	71.10
VYTORIN (10/10-10/20-10/40-10/80	1.75/1.64/1.65/1.75	52.50/49.20/49.50/52.50
Lova 20 + Eze 10	1.69	50.70
Lova 40-80 +Eze 10	1.69-1.95	50.70-58.50
Atorva 10 + Eze 10	2.81	84.30
Atorva 40 + Eze 10	3.63	108.90
Atorva 80 + Eze 10	3.49	104.70
Simva 10 + Colestipol 10 **Simva 10 + Cholestry 8**	1.61 (bulk) 0.59 (bulk)	48.30 (bulk) 17.70 (bulk)
Simva 40 + Colestipol 10	2.04 (bulk)	61.20 (bulk)

Simva 40 + Cholestry 8	1.02 (bulk)	30.60 (bulk)
Simva 80 + Colestipol 10	2.28 (bulk)	68.40 (bulk)
Simva 80 + Cholestyr 8	1.26 (bulk)	37.80 (bulk)
Simva 10 + Niaspan 2 g	1.11	33.30
Simva 40 + Niaspan 2 g	1.54	46.20
Simva 80 + Niaspan 2 g	1.78	53.40
ADVICOR (Lovastatin 20/Niaspan 1000 mg)	0.61	18.30

*Pricing dependent upon packaging purchased (e.g. Colestipol 500 mg in 5gm/packet or 5 gm x 90, cholestyramine 4 gm/5 gm 378 gm bulk (Sandoz) or 4 gm/5gm packets-(Teva generic)). +Pricing based upon 1000mg tablets. (Prices as of 4-15-05)

Pharmacoeconomic Analysis

To date, there have been two published pharmacoeconomic analyses evaluating statin monotherapy versus combination therapy with ezetimibe. At this time, there are no pharmacoeconomic analyses examining the cost-effectiveness of other lipid lowering combinations versus combinations involving ezetimibe.

In the first analysis, a pharmacoeconomic model was developed using clinical trial and epidemiologic data to predict lifetime benefit and cost of add-on treatment with ezetimibe in CHD (coronary heart disease) or non-CHD diabetic patients taking statins versus statins alone. In the model, three statin monotherapy strategies were compared with an ezetimibe-statin combination. In the model, it was assumed that improvements in the patient's lipid profile would extend life years due to a reduced rate of fatal CHD events. In the first strategy, the combination was compared to a static statin dose. In the second, the combination was compared to forced titration to maximum doses if LDL-C goals were not reached. In the third, the combination was compared to variable rates of statin titration based upon titration rates observed in cohorts of patients in medical practices in Spain, Germany and Norway. Reduction in LDL-C was assumed to be >20% with addition of ezetimibe and 7-11% with doubling of statin doses.[33] The authors caution that the results are only applicable to the populations studied.

In the analysis, the model predicted that an additional 14% of patients would meet their LDL-C goals with combination therapy versus statins alone. It was determined that the incremental cost-effectiveness ratio for ezetimibe plus statins would be <50,000 euros (just over 66,000 US) per life year gained for all comparisons. The criticism of this analysis is that we do not have any clinical outcome data for ezetimibe and it is difficult to know if addition of ezetimibe is more beneficial than titration of statin doses in terms of reducing CHD events. In addition, the reductions in LDL-C used for add-on ezetimibe (>20%) originated from one study (Gagne 2002) while the majority of published studies examining the combination demonstrate <20% additional reduction in LDL-C. It is also difficult to determine the reasons for the significant expense to adding ezetimibe as opposed to titrating statins. It is most likely due to the estimated increase in life years and the cost of ezetimibe.

In the second analysis, annual drug cost for statins and statins plus ezetimibe were presented. The costs were correlated with expected LDL-C lowering percentages for individual doses of statins and statins combined with ezetimibe. The authors reported that in patients requiring LDL-C reductions in excess of 55%, only simvastatin 40 mg and 80 mg plus ezetimibe or atorvastatin 80 mg plus ezetimibe are capable of reductions of this magnitude. Of these, simvastatin 40 mg plus ezetimibe was the least expensive combination.[34]

Conclusions

Ezetimibe is the first member of a new class of cholesterol lowering agents referred to as the cholesterol absorption inhibitors. At a dose of 10 mg daily, ezetimibe can reduce LDL-C by approximately 18%. When combined with atorvastatin, lovastatin, pravastatin or simvastatin, ezetimibe can generally reduce LDL-C an additional 12-15% (up to 20%) compared to the statin alone. When combined with a statin versus a statin alone, ezetimibe lowered triglycerides an additional 7-13% and raised HDL-C an additional 1-5%. Similar to the BAS and niacin, ezetimibe combined with a low dose statin can produce similar LDL-C lowering as quadruple the statin dose (e.g. simva 10 mg + ezetimibe 10 mg = simva 80 mg daily).

However, since most of the large health outcome statin trials utilized higher statin doses, it is not known whether the same clinical benefit will be seen if a low dose statin is combined with ezetimibe or another agent.

At this time, there is no evidence with ezetimibe monotherapy or when combined with a statin to support a reduction in cardiovascular health outcomes (nonfatal myocardial infarction, coronary heart disease death, etc). However, there is currently one clinical outcomes trial (IMPROVE-IT) and one atherosclerotic progression trial (ENHANCE) that are underway to determine the incremental benefit of adding ezetimibe to statins. Those data will not be available for a couple of years.

Ezetimibe appears to be well tolerated in combination with statins. However, in the majority of published trials, there was a numeric increase in the risk for clinically significant LFT elevation with ezetimibe in combination with statins versus statins alone. As a result, monitoring of LFTS in patients receiving combination therapy is recommended. Secondly, there have been several reports of myopathy after the addition of ezetimibe to high-dose statin therapy. As a result, caution should be used when choosing the combination especially in patients at risk for muscle toxicity from statins (advanced age, renal or liver impairment, hypothyroidism, frailty, female gender, alcoholism, drug-drug interactions, etc.).

Recommendations

Ezetimibe to remain nonformulary at National and VISN levels with alterations in current criteria for use:

Combination therapy
In patients not achieving their LDL-C goals with high-dose statins or the highest recommended or tolerated statin dose, clinicians are advised to consider add-on therapy with niacin. In HATS (HATS-Brown 2001), the combination of statins plus niacin led to regression of atherosclerosis and a relative reduction in clinical events of 90%. However, there are some patients that may not be candidates for niacin including those with a history of documented peptic ulcer disease, gouty attacks and/or poorly controlled diabetes. In those patients not reaching their LDL-C goals with add-on niacin; unable to tolerate niacin; or are not candidates for niacin, addition of either a BAS or ezetimibe (nonformulary) can be considered.

Monotherapy
Ezetimibe should not be considered first line for patients with elevated LDL-C who cannot tolerate statins since there are other lipid-lowering therapies (niacin or BAS) with clinical trial evidence to support reductions in CHD outcomes. However, ezetimibe may be considered as monotherapy in patients unable to tolerate statins and having an inadequate LDL-C lowering response, intolerance or contraindication to niacin and BAS.

Due to the potential variability in response to cholesterol absorption inhibitors, and since the maximum LDL-C response from ezetimibe can be seen as early as the first 2 weeks, assessment of response should be made within the first month of therapy. Monitoring of LFTs is recommended with the ezetimibe-statin combination.

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Appendix A. Studies Involving Ezetimibe and Statin Combinations

Clinical Trial	Population	Intervention	Results	Comments
Gagne, et al[21] MC, R, DB, PC 8 weeks	769 patients with primary hypercholesterolemia not achieving LDL-C goals on statins alone. Baseline LDL-C: 139 mg/dL	Ezetimibe 10 mg or placebo added to open-label statin	**% Change from Baseline** LDL: Ez+S -25.1; PL+S -3.7 HDL: Ez+S +2.7; PL+S +1 TG: Ez+S -14; PL+S -2.9 *p<0.001 for LDL and Trig, p<0.05 for HDL all in favor of EZ + S. LDL-C reduced an additional 21% with combo.	>70% of patients were receiving atorva or simva. Additional LDL-C reductions with Ez were similar for each statin. Clinically significant LFT elevation occurred in 4 Ez+S vs. 1 PL+S
Gagne, et al[22] MC, R, DB, PC 12 weeks	50 patients with homozygous familial hypercholesterolemia on atorva 40 or simva 40 with (25) our without (25) LDL apheresis were randomized to 1 or 3 groups Baseline LDL-C: S 80: 339 mg/dL Ez+S40/80: 313 mg/dL	1) Atorva or Simva 80 2) Ez 10 + Atorva 40 or Simva 40 3) Ez 10 + Atorva 80 or Simva 80	**% Change from Baseline (S40)** LDL: S 80 -6.7; Ez+S40/80 -20.7; Ez+S80 -27.5 HDL: S 80 +4.4; Ez+S40/80 -1.2; Ez+S80 NR TG: S 80 -5.8; Ez+S40/80 -10.8; Ez+S80 NR P=0.007 for LDL, no difference for HDL or TG. Authors report that Ez combined with statin 40 mg resulted in a 12.8% reduction in LDL-C.	Results for Ez+statin 40 and 80 mg were combined. Interestingly, the HDL-C was reduced in the ezetimibe+statin group. The changes in HDL-C were not separated by statin or dose. Patients weren't stratified based upon whether or not they were receiving LDL apheresis, although the investigators stated this did not make a difference.
Lipka, et al[23] MC, R, DB, PC 12 weeks	1861 younger and older patients with primary hypercholesterolemia. Baseline LDL-C: 178 mg/dL	1) Placebo 2) Statin or 3) Ez+Statin Statin doses: lova or prava 10, 20 or 40 mg, atorva or simva 10, 20, 40 or 80 mg	**%LDL-C Lowering Difference Between Statin alone and Ez + Statin by Age (All differences favor combo)** <65: -12.8 ≥65: -15.5 <75: -13.5 ≥75: -14.5 Combo reduced TG 27-29% vs. 16-20% with statins and increased HDL-C by 8-11% vs. 5-6% with statins alone.	Data from 4 studies were pooled in the analysis. LFT elevation occurred in 0.4% statin vs. 1.8% combination (<65 y/o)
Ballantyne, et al[24] R, DB, PC 12 weeks	628 patients with primary hypercholesterolemia Baseline LDL-C: 175-184 mg/dL	1) Placebo 2) Ez 10 mg 3) Atorva 10-80 4) Atorva 10-80 +Ez	**% Change from Baseline** LDL: Placebo 5.9; Ez -18.4; Atorva -42.4; A+Ez -54.5 HDL: Placebo 3.7; Ez +4.2; Atorva +4.3; A+Ez +7.3 TG: Placebo -6.4; Ez -5.1; Atorva -24.5; A+Ez -32.8 LDL-C reductions represent pooled atorva doses for analysis. P<0.01 in favor of combination group for all comparisons (LDL, HDL, TG). Combo provided an additional 12.1% reduction in LDL-C	As seen in previous studies with atorva 80 mg, elevation in HDL seen with lower doses was reduced with 80 mg. However, combo of ezetimibe with atorva maintained HDL increase. One patient on combo experienced CK>10 X ULN. 1% on atorva vs. 2% on combo had LFTs >3 X ULN
Ballantyne, et al[25] MC, R, DB 24 weeks	788 patients with hypercholesterolemia Baseline LDL-C: 180 mg/dL	Forced titration through 4 periods each 6 weeks. 1) Atorva 10, 20, 40 and 80 2) Ez+Simva 10/20, 10/20, 10/40, 10/80 3) Ez+Simva 10/20, 10/40, 10/40, 10/80	**% Reduction from Baseline** Period/Dose: 1-A 10; 2-A 20; 3-A 40; 4-A80; 1-10/10; 2-10/20; 3-10/40; 4-10/80 LDL: -37.2; -44.3; -49.1; -52.5; -46.1; -50.3; -55.6; -59.4 HDL: 5.1; 6.9; 7.8; 6.5; 8; 9.5; 11.4; 12.3 TG: -22.5; -28.4; -31.2; -34.8; -26.3; -24.6; -32; -35.5 LDL-C reduction (averaged across the dose range) was 52.4% for the combo and 45.1% for atorva (p<0.001). HDL-C elevation was also statistically greater in favor of the combo. TG differences weren't significant.	Incidence of elevated LFTs did not differ between groups (2-2.4%). CK elevation >10 X ULN occurred and without symptoms occurred in 2 patients on combo (10/20 and 10/40) and one with symptoms on the combo of 10/80.
Ballantyne, et al[26] MC, R, DB 6 weeks	1902 patients with hypercholesterolemia Baseline LDL-C: 175-182 mg/dL	1) Atorva 10, 20, 40 or 80 mg or 2) Ez 10 + Simva 10, 20, 40 or 80 mg as the combo product (Vytorin)	**% Reduction from Baseline** Drug/Dose: A 10; A 20; A 40; A80; 10/10; 10/20; 10/40; 10/80 LDL: -36.1; -43.7; -48.3; -52.9; -47.1; -50.6; -57.4; -58.6 HDL: 6.9; 5.1; 3.8; 1.4; 7.7; 7.2; 9; 12.8 TG: -21.3; -24.8; -23.6; -32.1; -25.5; -25.4; -27.3; -30.8 LDL-C reduction, averaged across doses, were 53.4 with combination vs. 45.3% with	Authors comment that at the highest doses (Ez 10/Simva 80 or Atorva 80), a similar percentage of patients met an LDL-C goal of <100. However, for the more aggressive goal of <70 mg/dL, 64% of the combo vs. 36% of high dose atorva met this more aggressive goal. A statistically greater number of patients on atorva had clinically

<table>
<tr><td></td><td></td><td></td><td>atorvastatin. (p<0.001 in favor of combo). HDL elevation statistically favored combo. No difference for TG lowering.</td><td>significant elevation in LFTs vs. combo (1.2% vs. 0.1%, respectively, p=0.006). No patient withdrew from the study for myopathic symptoms or CK elevation.</td></tr>
<tr><td>Kerzner, et al[27]
MC, R, DB, PC
12 weeks</td><td>548 patients with primary hypercholesterolemia

Baseline LDL-C: 176-178 mg/dL</td><td>1) Placebo
2) Ez 10
3) Lova 10, 20, or 40 mg
4) Ez 10 + Lova 10, 20 or 40 mg</td><td>% Change from Baseline<table><tr><td></td><td>LDL</td><td>HDL</td><td>TG</td></tr><tr><td>Placebo</td><td>0</td><td>0</td><td>-4</td></tr><tr><td>Ez</td><td>-19</td><td>3</td><td>-3</td></tr><tr><td>Lova</td><td>-25</td><td>4</td><td>-11</td></tr><tr><td>Ez+Lova</td><td>-39</td><td>9</td><td>-22</td></tr></table>Percentages reflect pooled doses of Lova. Combination reduced LDL-C by an additional 14% and statistically more than either therapy alone (p<0.01).</td><td>Only 1 patient in the combination group had clinically significant elevation in LFTs (Ez10+Lova 10). No patient had CK elevation >10 X ULN</td></tr>
<tr><td>Melani, et al.[28]
MC, R, DB, PC
12 weeks</td><td>538 patients with primary hypercholesterolemia

Baseline LDL-C: 178 mg/dL</td><td>1) Placebo
2) Ez 10
3) Prava 10, 20 or 40
4) Ez + Prava 10-40</td><td>% Change from Baseline<table><tr><td></td><td>LDL</td><td>HDL</td><td>TG</td></tr><tr><td>Placebo</td><td>1.3</td><td>2</td><td>2</td></tr><tr><td>Ez</td><td>-18.7</td><td>4.1</td><td>-2.1</td></tr><tr><td>Prava</td><td>-24.3</td><td>6.7</td><td>-7.6</td></tr><tr><td>Ez+Prava</td><td>-37.7</td><td>8.1</td><td>-17.6</td></tr></table>Percentages reflect pooled doses of Prava. Combination reduced LDL-C by an additional 13.4% vs. prava alone and statistically more than either therapy alone (p<0.01). Combo reduced TG significantly more than either monotherapy and increased HDL more than ezetimibe alone.</td><td>Authors reported serious ADEs were rare and occurred with a similar frequency.

LFT elevation occurred in 2 patients on prava alone and 2 on the combination. CK elevation > 10 X ULN was observed in 2 patients on prava monotherapy.</td></tr>
<tr><td>Davidson, et al.[29]
MC, R, DB, PC
12 weeks</td><td>668 patients with primary hypercholesterolemia

Baseline LDL-C: 176-181 mg/dL</td><td>1) Placebo
2) Ez 10
3) Simva 10, 20, 40 or 80
4) Ez 10 + Simva 10-80 mg</td><td>% Change from Baseline<table><tr><td></td><td>LDL</td><td>HDL</td><td>TG</td></tr><tr><td>Placebo</td><td>-1.3</td><td>0.9</td><td>2.4</td></tr><tr><td>Ez</td><td>-18.1</td><td>5.1</td><td>-8.3</td></tr><tr><td>Simva</td><td>-36.1</td><td>6.9</td><td>-16.6</td></tr><tr><td>Ez+Simva</td><td>-49.9</td><td>9.3</td><td>-24.1</td></tr></table>Percentages reflect pooled doses of Simva. Combination reduced LDL-C by an additional 13.8% vs. Simva alone and statistically more than either therapy alone (p<0.01). TG reductions were in favor of combination vs. either therapy alone (P<0.001). HDL-C elevation was also statistically higher in combo group.</td><td>Discontinuation due LFT elevation occurred in 2 patients on simva monotherapy and 6 patients on combination therapy. CK elevation >10 X ULN was observed in 2 patients on simva alone.</td></tr>
<tr><td>Goldberg, et al.[30]
MC, R, DB, PC
12 weeks</td><td>887 patients with primary hypercholesterolemia

Baseline LDL-C: 174-176 mg/dL</td><td>1) Placebo
2) Ez 10
3) Simva 10, 20, 40, or 80
4) Ez 10 + Simva 10-80</td><td>% Change from Baseline<table><tr><td></td><td>LDL</td><td>HDL</td><td>TG</td></tr><tr><td>Placebo</td><td>2.7</td><td>2.3</td><td>-2.2</td></tr><tr><td>Ez</td><td>-19.8</td><td>7</td><td>-13.2</td></tr><tr><td>Simva</td><td>-38.5</td><td>7.6</td><td>-15.2</td></tr><tr><td>Ez+Simva</td><td>-53.2</td><td>8.2</td><td>-28</td></tr></table>Percentages reflect pooled doses of Simva. Combination reduced LDL-C by an additional 14.8% vs. Simva alone and statistically more than either therapy alone (p<0.01). TG reduced significantly more in the combo group vs. pooled simva (p<0.001) but HDL not different.</td><td>Discontinuation due to ADEs were numerically more frequent in the combination group compared to the other groups (5% vs. 2-3%, respectively). LFT elevation occurred in 6 patients (2%) on the combination vs. none in the other groups. This led to discontinuation in 5. Clinically significant CK elevation occurred in 1 (1%) on placebo, 1 (0.3%) on simva, 2 (0.6%) on combination.</td></tr>
<tr><td>Feldman, et al.[31]
MC, R, DB
23 weeks</td><td>710 patients with CHD or risk equivalent disease

Baseline LDL-C: 165-173 mg/dL</td><td>1) Simva 20
2) Simva 10 + Ez 10
3) Simva 20 + Ez 10
4) Simva 40 + Ez 10
Doses titrated at weeks 6, 12 and 18 up to max of 80 if LDL not <100</td><td>Primary Efficacy Measure was LDL-C lowering with Simva 20 vs. Simva 20 + Ez 10.
% Change from Baseline (first 6 weeks)<table><tr><td></td><td>LDL</td><td>HDL</td><td>TG</td></tr><tr><td>Simva 20</td><td>-38</td><td>5.1</td><td>-19</td></tr><tr><td>Simva 10+Ez</td><td>-47</td><td>6.2</td><td>-19</td></tr><tr><td>Sim20+ Ez</td><td>-53</td><td>8</td><td>-25</td></tr></table></td><td>Signficantly more patients achieved an LDL-C of <100 mg/dL in the combination group compared to simva alone. However, at the end of the study, a certain percentage of patients had not met their goals but only a small number were further titrated.

Two patients receiving combination vs. none on simva</td></tr>
</table>

			Sim40 +Ez	-59	7.4	-30	alone experienced clinically significant LFT elevation. These 2 patients completed the study. Clinically significant CK elevation occurred in 2 on simva alone vs. 1 on combination therapy. No cases of rhabdomyolysis were reported.

% of Patients with LDL-C Goal of <100 mg/dL

	After six weeks	End of study	% Requiring titration
Simva 20	46%	59%	68%
Simva 10+Ez	75%	78%	33%
Sim20+ Ez	83%	83%	22%
Sim40 +Ez	87%	86%	12%

Mean dose of Simva: 50.3, 20.2, 27.7, 44.9, respectively.

A=atorvastatin, ADE=adverse events, DB=double-blind, Ez=ezetimibe, LFTs=liver function tests, MC=multicenter, NR=not reported, PL=placebo, R=randomized, S=statin, S40=statin at 40 mg daily, Sim=simvastatin, TG=triglycerides, ULN=upper limit of normal

Appendix B Studies Involving Combination with Statins and Niacin

Statin+Niacin Atherosclerotic Progression Trials

Clinical Trial	HATS 2001	Arbiter-2-2004	Hecht, HS 2005
N	160-RCT	167-RCT	162-Observational study
Population	Men <63, Women <70, known CAD, HDL<35 men, <40 women, LDL <145, TG <400	Men and women >30, known CVD, LDL <130, HDL <45 **on statins**, mostly simva ≥20 mg/day	Men and women **w/o** known CAD but evidence of subclinical atherosclerosis
Intervention	**Simva 10-20+Niacin 2g** or Antioxidant vits, the combination or placebo	Addition of Niaspan 1 g or placebo to background statins	Statins (atorva, simva or prava) or statins + Niaspan 1897 mg/day (mean)
Duration	3 years	1 year	1.2 years
Method Measuring Progression	Arteriography: left and right coronary arteries	Carotid B-mode ultrasound (intima-media thickness)	Electron Beam Tomography - (EBT) calcified plaque
Progression/Regression	Regressed 0.4% in simva-niacin (p<0.001) vs. placebo	Increase in CIMT niacin vs. placebo (p=0.08). Post-hoc subgroup=those on niacin w/o insulin resistance, IMT progressed less (p=0.026)	NS
LDL/HDL/TG (change from baseline)	-42%/+26%/-36%	-3%/21%/13%	-41%/+25%/-26.5%
Outcomes (Death CHD or other, MI, Revascul-arization, stroke	Simva-niacin RRR 90% reduction in clinical events (p=0.03)	NS with addition of niacin vs. placebo (p=0.20)	NR
Comments	Antioxidant vitamins lessened the benefit of simva-niacin combo.	149/167 were included in endpoint analysis	HDL was significantly lower and TG significantly higher in the combo group.

NR=not reported, NS=not significant, w/o=without