Clinician Medication Summary
Ezetimibe (Zetia) & ezetimibe/simvastatin (Vytorin)

GroupHealth

- **Statin monotherapy should be maximized before any other lipid-lowering options are considered because statins have the best evidence of impact on clinically important outcomes.**
- **Monotherapy ezetimibe reduces LDL cholesterol by 18-20% on average. No outcome trials have been conducted to provide evidence of true clinical benefit.**
- **Two outcome trials have compared ezetimibe/simvastatin to placebo. The SEAS trial did not show a benefit in patients with aortic stenosis. The SHARP trial did show a statistically significant benefit in patients with chronic kidney disease (CKD) compared to placebo.**
- **Outcome studies with ezetimibe and ezetimibe/simvastatin vs. an alternate active comparator have not been studied.**

Efficacy

- The SEAS trial did not show a significant decrease in major cardiovascular events in patients with aortic stenosis when ezetimibe 10 mg/simvastatin 40 mg was compared to placebo.
- The SHARP trial showed a reduction in major atherosclerotic events in CKD patients taking ezetimibe 10 mg/ simvastatin 20 mg when compared to placebo with a number needed to treat of 48 over 5 years to prevent one event. Since simvastatin has been proven to reduce cardiovascular events in previous trials, the benefit of ezetimibe in this trial is unknown.
- The ENHANCE trial did not show a significant change in the intermediate marker of carotid artery intima media thickness when ezetimibe 10 mg/simvastatin 80 mg was compared to simvastatin 80 mg alone. The trial was not large enough to assess clinically important outcomes.
- Atorvastatin 80 mg and ezetimibe 10 mg/simvastatin 40 mg have comparable LDL lowering effect (~55% reduction).
- Atorvastatin 80 mg and simvastatin 40 mg have evidence of decreasing true clinical outcomes, evidence which is not available for ezetimibe and ezetimibe/simvastatin.

Ref	Outcome	Simva40/E10	Placebo	HR (95% CI)	ARR	NNT
Rossebø 2008 (SEAS)	Major CV event	35.3%	38.2%	0.96 (0.83-1.12) p=0.59 (NS)	NS	NS
Baigent 2011 (SHARP)	Major atherosclerotic event	11.3%	13.4%	0.83 (0.74-0.94) p=0.0021	2.1%	48 over 5 years
Kastelein 2008 (ENHANCE)	Change in carotid artery intima media thickness	0.0111 mm	0.0058 mm	p=0.29 (NS)	N/A	N/A

HR–Hazard Ratio, RR–Risk Ratio, ARR–Absolute Risk Reduction, NNT–Number Needed to Treat to benefit one person, NS–Not Significant, N/A–Not Applicable

Safety

- Ezetimibe is generally well tolerated and has a mild side effect profile (based on short-term trials).
- In post-marketing reports, ezetimibe has been rarely associated with myalgia, hepatitis, acute pancreatitis, thrombocytopenia, and rhabdomyolysis.
- The SEAS trial found a significantly higher risk ($p = 0.01$) of cancer in patients taking simvastatin/ezetimibe (11.1%) versus those taking placebo (7.5%). The SHARP trial did not find such an increase in chronic kidney disease patients.
- Do not prescribe new prescriptions for ezetimibe 10 mg/simvastatin 80 mg (per June 2011 ezetimibe/simvastatin label change). It is safe to continue prescribing this medicine for patients on therapy for at least one year without evidence of myalgias or not affected by interacting medicines.

Other Important Information

- For primary prevention, the Group Health ASCVD guideline supports a target LDL of <130 mg/dL for patients without diabetes.
- Consider an LDL goal <100 mg/dL, if it can be achieved with a statin, for patients with diabetes who have a 5-year risk of CVD >10% or who are age 40 years and older.
- For secondary prevention, the Group Health ASCVD guideline supports a target LDL of <100 mg/dL or <70 mg/dL, based on clinical judgment of benefits vs. risk of treatment.

Cost Comparison to other Group Health Commercial Formulary Alternatives

Drug (Formulary status)	Average Daily Dose	Average % LDL reduction	Patient Cost for 30 Day Supply Without Rx Coverage*
Ezetimibe (Zetia) [F-PA]†	10 mg once daily	18-20%	$135
Ezetimibe/ simvastatin (Vytorin) [F-PA] †	10 mg/40 mg once daily	55%	$135
Simvastatin [F]	40 mg once daily	41%	$ 28
Atorvastatin (Lipitor) [F/NF]‡	80 mg once daily	55%	$158
Lovastatin [F]	40 mg once daily	34%	$36
Pravastatin [F]	80 mg once daily	37%	$120
Rosuvastatin (Crestor) [NF]	40 mg once daily	53%	$157

F = Formulary, F-PA = Formulary with Prior Authorization; NF = Non-formulary
*Prices obtained from Drugstore.com as of 8/22/11
†Will become NF (with exception criteria) effective November 2011; ‡Atorvastatin 40 mg and 80 mg are F, 10 mg and 20 mg are NF

References

- Rossebø AB, Pedersen TR, Bowman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *NEJM* 2008;359:1343-56
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- Kastelein JJ, Akdim F, Stroes ESG, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *NEJM* 2008;358:1431-43
- Law MR, Wald NJ, Rudnicka AR. Quantifying effects of statins on low density lipoprotein cholesterol, ischemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;326:1423-29
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