

Ezetimibe/Ezetimibe plus Simvastatin (Zetia®/Vytorin®)

Criteria for Use (Update)

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

Pharmacy should use this document as guidance and not for rigid enforcement.

The Product Information should be consulted for detailed prescribing information.

Exclusion Criteria *If ANY of the boxes below are checked, then the patient should NOT receive ezetimibe.*

The following contraindications apply when ezetimibe is to be combined with a statin:¹

- Patient has active liver disease or unexplained persistent elevation in hepatic transaminases
- Pregnancy or a woman who may become pregnant since combination with a statin may cause fetal harm. *(Pregnancy must be excluded prior to receiving ezetimibe plus statins and the patient provided contraceptive counseling on potential risk vs. benefit of taking ezetimibe with statins if patient were to become pregnant. If ezetimibe is not combined with a statin, evidence is lacking in pregnant women and therefore ezetimibe [as single lipid modifying therapy] should be used only if the potential benefit justifies the risk to the fetus.)*
- Patient is a nursing mother

The following contraindications apply with ezetimibe +/- statin

- Patient with a known hypersensitivity to any component of ezetimibe

Inclusion Criteria *One of the following must be fulfilled in order to meet criteria.*

Ezetimibe in Combination with a Statin:

NOTE: *Therapy with statins should be maximized prior to considering addition of ezetimibe to a moderate dose statin.*

- Patients with acute coronary syndrome, known coronary artery disease with multiple uncontrolled risk factors or recurrent atherosclerotic cardiovascular disease (ASCVD) on moderate dose statins who are unable to tolerate high dose statins* or in those patients with factors that preclude them from using maximum statin doses (e.g., drug-drug interactions, etc.).

NOTE: *Evidence is lacking to support whether there is a difference between moderate dose statins plus ezetimibe and high dose statins in reducing ASCVD events in any population. Additionally, there is a lack of evidence to support that addition of ezetimibe to high dose statin therapy further reduces ASCVD events (See issues for consideration) or whether ezetimibe added to low dose statins reduces clinical events in patients who are unable to tolerate moderate doses.*

*High dose statins: atorvastatin 40-80 mg, rosuvastatin 20-40 mg

Monotherapy with Ezetimibe:

- Patients treated for primary or secondary prevention who are unable to tolerate statins (e.g., after a therapeutic trial of at least 3 different statins [e.g., simvastatin, atorvastatin and rosuvastatin]).

Prior to considering monotherapy with ezetimibe in statin intolerant patients, first consider monotherapy with gemfibrozil, niacin or bile acid sequestrants since these agents have shown a reduction in ASCVD events in limited populations (See issues for consideration). There is no evidence that ezetimibe as single drug therapy reduces ASCVD events.

In patients unable to tolerate statins, alternate-day statin dosing reduces LDL-C but there is a lack of evidence that this dosing strategy reduces ASCVD events. However when possible, statins should remain as first-line therapy in primary and secondary prevention and use of alternate-day statins may be considered in patients unable to tolerate daily statins.

Dosage and Administration¹

Ezetimibe 10 mg once daily as monotherapy or in combination with statins. Ezetimibe can be taken with or without food.

Monitoring

- Baseline liver function testing should be performed prior to initiation of ezetimibe, when combined with statins, and then if symptoms suggestive of liver toxicity arise (e.g., unusual fatigue or weakness; loss of appetite; upper belly pain; dark-colored urine; yellowing of the skin or sclera).
- Patients should be instructed to report any unexplained muscle, pain or weakness while receiving ezetimibe combined with statins.

Issues for Consideration**Summary of the IMPROVE-IT Trial**

- The IMPROVED Reduction of Outcomes: Vytorin Efficacy International (IMPROVE-IT) Trial was designed to determine whether addition of ezetimibe 10 mg daily to simvastatin 40 mg daily in patients with acute coronary syndrome (ACS) leads to additional clinical benefit in further reducing major cardiovascular events when compared to simvastatin 40 mg daily.¹
- Eligible patients were randomized within 10 days of their ACS event; inclusion criteria were as follows: 50 years and older, LDL of at least 50 mg/dL and not greater than 125 mg/dL in patients not on lipid lowering therapy and not greater than 100 mg/dL in those receiving lipid lowering therapy. Goal of therapy was to have LDL-C <70 mg/dL in both groups.
- Between October 2005-July 2010, 18,144 patients were randomized to 1149 sites in 39 countries. Baseline characteristics did not differ between groups and included a mean age of 63 years, 75% were males and 84% of patients were white. The majority of patients were residents of North America or Western Europe (78%). Before the index event, nearly 35% were on a statin and 42% on ASA. Index event was a myocardial infarction (MI) in 75% of patients and mean LDL-c at randomization was 94 mg/dL. At the time of randomization, 97% were on ASA, 86% on a thienopyridine, 86% on a beta-blocker and 75% on an angiotensin converting enzyme inhibitor or angiotensin receptor blocker.
- Median follow up was 6 years.
- There were 4 composite endpoints (Primary composite and three secondary composite outcome measures-see table)

Outcome	Simva + Placebo (n=9077)	Simva+Ezetimibe (n=9067)	Hazard Ratio (95% CI)	P Value
PRIMARY ENDPOINT				
Death from cardiovascular (CV) causes, major coronary event or nonfatal stroke	2742 (34.7%)	2573 (32.7%)	0.936 (0.89-0.99)	0.016 NNT=50
SECONDARY ENDPOINTS				
Death from any cause, major coronary event or nonfatal stroke	3246 (40.3%)	3089 (38.7%)	0.95 (0.9-1.0)	0.03 NNT=62.5
Death from coronary heart disease (CHD) nonfatal MI, urgent coronary revascularization ≥30 days	1448 (18.9%)	1322 (17.5%)	0.91 (0.85-0.98)	0.02 NNT=71
Death from CV causes, nonfatal MI, hospitalization for unstable angina, all revascularization ≥30 days and nonfatal stroke	2896 (36.2%)	2716 (34.5%)	0.95 (0.9-1.0)	0.04 NNT=59
SELECTED TERTIARY ENDPOINTS				
Death from any cause	1231 (15.3%)	1215 (15.4%)	0.99 (0.91-1.07)	0.78
Death from CV causes	538 (6.8%)	537 (6.9%)	1 (0.89-1.13)	1.00
Death from CHD	461 (5.8%)	440 (5.7%)	0.96 (0.84-1.90)	0.5
Any MI	1118 (14.8%)	977 (13.1%)	0.87 (0.8-0.95)	0.002
Nonfatal MI	1083 (14.4%)	945 (12.8%)	0.87 (0.8-0.95)	0.002

Fatal MI	49 (0.7%)	41 (0.5%)	0.84 (0.55-1.27)	0.41
Any stroke	345 (4.8%)	296 (4.2%)	0.86 (0.73-1)	0.05
Ischemic stroke	297 (4.1%)	236 (3.4%)	0.79 (0.67-0.94)	0.008
Hemorrhagic stroke	43 (0.6%)	59 (0.8%)	1.38 (0.93-2.04)	0.11
Coronary revascularization	1793 (23.4%)	1690 (21.8%)	0.95 (0.89-1.01)	0.11
Urgent coronary revascularization	626 (8.6%)	510 (7%)	0.81 (0.72-0.91)	0.001
Any revascularization	1962 (25.6%)	1871 (24.2%)	0.96 (0.9-1.02)	0.18
Hospitalization for unstable angina	148 (1.9%)	156 (2.1%)	1.06 (0.86-1.33)	0.63

Revascularization=30 days or greater after randomization. Authors commented that the benefit of ezetimibe seemed to appear after 1 year of treatment.

- Addition of ezetimibe to simvastatin reduced LDL by about 24%. Median time-weighted LDL was 69.5 mg/dL in the simvastatin group vs. 53.7 mg/dL in the simvastatin + ezetimibe group ($p < 0.001$). Simvastatin was increased to 80 mg daily in 27% of the simvastatin + placebo vs. 6% of the simvastatin + ezetimibe group.
- In pre-specified subgroups, the addition of ezetimibe to simvastatin resulted in a more marked benefit in diabetic patients and those 75 years of age or older.
- Numbers of patients who withdrew from the study for any reason did not differ between groups. After a median of 6 years, 42% of patients had stopped the study drug, withdrew consent or were lost to follow up.
- There were no differences between groups in terms of elevated liver function tests (LFTs), rates of gall bladder related events, cholecystectomy, muscle-related adverse events or new, relapsing or worsening cancer. The percentage of patients withdrawing due to an adverse event occurred in 10.1% of simvastatin alone vs. 10.6% of patients receiving the combination. (See page 8 of the article for details on number of events).²
- In summary, the combination of simvastatin 40 mg plus ezetimibe 10 mg daily was associated with a 2% absolute risk reduction in the primary endpoint versus simvastatin 40 mg in patients with recent ACS followed over a median period of 6 years. Differences in the primary and secondary composite endpoints were limited to nonfatal events. The number of patients needed to treat with this combination over a period of 6 years to reduce one nonfatal ASCVD event was 50. That is, 1 of 50 patients would avoid a nonfatal event over 6 years of treatment while 49 would get no event reduction. Study drop out rates were high at 42% and reasons for discontinuation between the two groups were similar. Rates of cancer, gallbladder or muscle events or increased LFTs did not differ between groups.

Other Issues for Consideration:

- Statins should be considered first-line for patients treated for primary or secondary prevention.
- Treatment with statins should be maximized prior to considering combination therapy with ezetimibe.
- A high dose statin is recommended only in select patient populations (e.g., ACS, multiple uncontrolled risk factors or recurrent CVD events on a moderate dose statin) following a discussion of the added small harms, small additional benefits (see table below) and an exploration of the patient's values and preferences. Patients with recent ACS or recurrent ASCVD should be advised to take a moderate dose statin and consider increasing to a high dose statin as tolerated.

CTT Collaboration Meta-Analysis of Twenty-Six Clinical Trials (Safety and Efficacy) and ACC/AHA Evidence Summary (Moderate vs. High Intensity Statin)^{3,4}

Outcome	Moderate Intensity (Events/N)	High Intensity (Events/N)	NNT or NNH
Rhabdomyolysis^{4*}	1/10,000	4/10,000	--
Diabetes³	1/1000 treated for 1 yr	3/1000 treated for 1 yr	NNH 498
First Major Cardiovascular Event⁴	5.3%/year	4.5%/year	ARR 0.8%, NNT 125
Major CVD Events³	--	6.5 fewer events/1000 pts treated for 1 year vs. moderate dose statins	NNT 155

ACC/AHA=American College of Cardiology/American Heart Association, ASCVD=atherosclerotic cardiovascular disease, CTT=Cholesterol Treatment Trialists', N=number, NNH=number need to harm during a given time for one adverse event to occur, NNT=number needed to treat during a given time for one less event to occur. *Rhabdomyolysis was increased in the simvastatin 80 mg groups compared to moderate intensity

statins (A to Z and SEARCH).

- Other situations where a high dose statin may be reasonable or desirable for LDL-C lowering but a patient is unable to tolerate high dose statins (e.g., uncontrolled diabetes with ASCVD or patients with ASCVD unable to achieve a 30-50% reduction in LDL-C with moderate dose statins) should be adjudicated on a case-by-case basis, as data in these populations are lacking.
- There are situations that may require additional LDL lowering in the presence of maximum dose statins (e.g., Familial Hypercholesterolemia or other hereditary syndromes). These cases may be adjudicated on a case-by-case basis.
- In patients treated for primary prevention who are unable to tolerate statins, reinforce adherence to positive lifestyle changes. If pharmacologic treatment is needed, consider treatment with gemfibrozil or bile acid sequestrants (BAS), recognizing that these agents have been associated with only a small CVD risk reduction and in limited study populations (e.g., males with LDL-C >190 mg/dL).
- In patients with established ASCVD who are unable to tolerate statins, it is important to reinforce lifestyle changes and consider offering niacin or gemfibrozil, recognizing that these agents have been associated with only a small cardiovascular disease (CVD) risk reduction in limited study populations (e.g., males with low HDL-C).
- Moderate dose statins: simvastatin 20-40 mg, atorvastatin 10-20 mg, pravastatin 40 mg, lovastatin 40-80 mg and fluvastatin 80 mg (80 mg XL or 40 mg twice daily), rosuvastatin 5-10 mg, pitavastatin 2-4 mg
- High dose statins: atorvastatin 40-80 mg and rosuvastatin 20-40 mg daily.
- There is evidence from short-term published trials showing a similar percent reduction in LDL-C from baseline between the 5 and 10 mg daily dose.⁵⁻⁷ Although some clinicians use a 5 mg rather than 10 mg dose of ezetimibe for lowering LDL-C, the lower dose regimen was not studied in IMPROVE-IT and as such, there is no evidence demonstrating clinical benefit at this dose.
- If ezetimibe is combined with BAS, ezetimibe should be taken 1-2 hours before or 4-6 hours after the BAS.

Renewal Criteria

- There is potential variability in response to cholesterol absorption inhibitors (ezetimibe). Generally, response to new lipid-lowering treatment should be gauged at two follow-up clinic visits. If a patient does not experience a substantive response after addition of ezetimibe (at least 10-15%), consider discontinuing ezetimibe.

Prepared: October 2015. Contact: Cathy Kelley Catherine.kelley@va.gov VA Pharmacy Benefits Management Services

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