

STEP THERAPY POLICY

POLICY: Zetia Step Therapy Policy

- Zetia® (ezetimibe tablets – Merck, generic)

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OVERVIEW

Ezetimibe, an inhibitor of intestinal cholesterol (and related phytosterol) absorption, is indicated as an adjunct to diet to:¹

- Reduce elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B) and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with **primary hyperlipidemia, alone or in combination with a hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin)**.
- Reduce elevated total-C, LDL-C, apo B, and non-HDL-C in patients with **mixed hyperlipidemia in combination with fenofibrate**.
- Reduce elevated total-C and LDL-C in patients with **homozygous familial hypercholesterolemia (HoFH)** in combination with atorvastatin or simvastatin.
- Reduce elevated sitosterol and campesterol levels in **homozygous sitosterolemia (phytosterolemia)**.

Nationally-recognized guidelines recommend statins first-line due to the robust LDL-lowering capacity and the extensive data that use of statins reduces cardiovascular morbidity and mortality in a variety of patient populations.^{2,3} Ezetimibe can be used with statins for additive LDL-lowering effects or as monotherapy. LDL-C lowering with ezetimibe generally ranges from 15% to 25%. For patients who cannot take or tolerate statins, ezetimibe is an alternative.

Safety

Ezetimibe is well-tolerated.¹⁻³ Rates of elevated hepatic transaminases are similar for placebo and ezetimibe monotherapy. Ezetimibe is not an inhibitor or an inducer of the cytochrome P450 (CYP) isozymes (e.g., 1A2, 2D6, 2C8/9, and 3A4) and it is unlikely that ezetimibe will impact the metabolism of medications metabolized by these enzymes.¹ Ezetimibe is in pregnancy category C.¹ All HMG CoA are known teratogens (Pregnancy Category X).¹⁻³ No excess myopathy or rhabdomyolysis was noted in clinical studies with ezetimibe.¹⁻³ This may be important in patients who have conditions related to underlying neuromuscular disease (e.g., McArdle disease, muscular dystrophies).^{4,5}

POLICY STATEMENT

This program has been developed to encourage the use of a Step 1 drug prior to the use of the Step 2 drug, and the use of the Step 2 drug prior to the use of the Step 3 drug. If the Step Therapy rule is not met for the Step 2 drug or the Step 3 drug at the point of service, coverage will be determined by the Step Therapy criteria below. All approvals are provided for 1 year in duration.

Automation: A patient with a history of one Step 1 drug within the 130-day look-back period can receive the Step 2 drug. A patient with a history of one Step 1 drug and the Step 2 drug within the 130-day look-back period can receive the Step 3 drug.

Step 1: generic or brand hydroxyl-methylglutaryl-coenzyme A (HMG)/HMG combination products (i.e., lovastatin, simvastatin, pravastatin, fluvastatin, fluvastatin extended-release, atorvastatin, rosuvastatin, atorvastatin plus amlodipine; ezetimibe plus simvastatin, Lipitor, Lescol, Lescol XL, Altoprev, Pravachol, Crestor, Ezallor, Mevacor, Zocor, Livalo, Zypitamag, Caduet, Vytorin, Flolipid)

Step 2: generic ezetimibe tablets

Step 3: brand-name Zetia

CRITERIA

1. Approve the Step 2 drug (generic ezetimibe) for 1 year if the patient meets one of the following (A, B, C, D, E, F, G or H):
 - A) Patient has tried one Step 1 drug; OR
 - B) Generic ezetimibe is being initiated in combination with a Step 1 drug; OR
 - C) Patient is taking or will be taking a medication that has a significant drug-drug interaction with a Step 1 drug; OR
 - D) Patient has severe renal impairment; OR
 - E) Patient has homozygous sitosterolemia (phytosterolemia); OR
 - F) Patient is pregnant; OR
 - G) Patient has active liver disease or unexplained persistent elevations of serum transaminases; OR
 - H) Patient meets one of the following (i or ii):
 - i. Patient has been previously diagnosed with myopathy or rhabdomyolysis (either medication related or not medication related); OR
 - ii. Patient has an underlying muscle/muscle-metabolism related disorder.

2. Approve the Step 3 drug (brand Zetia) for 1 year if the patient meets both of the following (A and B):
 - A) Patient has tried the Step 2 drug (generic ezetimibe); AND
 - B) Patient meet one of the following (i, ii, iii, iv, v, vi, vii or viii):
 - i. Patient has tried one Step 1 drug; OR
 - ii. Brand Zetia is being initiated in combination with a Step 1 drug; OR
 - iii. Patient is taking or will be taking a medication that has a significant drug-drug interaction with a Step 1 drug; OR
 - iv. Patient has severe renal impairment; OR
 - v. Patient has homozygous sitosterolemia (phytosterolemia); OR
 - vi. Patient is pregnant; OR
 - vii. Patient has active liver disease or unexplained persistent elevations of serum transaminases; OR
 - OR

viii. Patient meets one of the following [(1) or (2)]:

- (1) Patient has been previously diagnosed with myopathy or rhabdomyolysis (either medication related or not medication related); OR
- (2) Patient has an underlying muscle/muscle-metabolism related disorder.

REFERENCES

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4. Luck RP, Verbin S. Rhabdomyolysis. A review of clinical presentation, etiology, diagnosis and management. *Pediatr Emerg Care.* 2008;24(4):262-268.
5. Bagley WH, Yang H, Shah KH. Rhabdomyolysis. *Intern Emerg Med.* 2007;2:210-218.