STEP THERAPY POLICY

POLICY: Ezetimibe Step Therapy Policy
- Zetia® (ezetimibe tablets – Organon, generic)

REVIEW DATE: 08/24/2022

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).

Guidelines

Nationally recognized guidelines recommend statins as first-line therapy 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.[2-4] 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.[1-4] 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 statins are known teratogens (Pregnancy Category X).[1-4] No excess myopathy or rhabdomyolysis was noted in clinical studies with ezetimibe.[1-5] This may be important in patients who have conditions related to underlying neuromuscular disease (e.g., McArdle disease, muscular dystrophies).[6-9]

POLICY STATEMENT

This program has been developed to encourage the use of a Step 1 Product prior to the use of the Step 2 Product, and the use of the Step 2 Product prior to the use of the Step 3 Product. If the Step Therapy rule is not met for the Step 2 Product or the Step 3 Product 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 Product within the 130-day look-back period can receive the Step 2 Product. A patient with a of one Step 1 Product and the Step 2 Product within the 130-day look-back period can receive the Step 3 Product.

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

Step 2: generic ezetimibe tablets

Step 3: brand-name Zetia

CRITERIA

1. Approve the Step 2 Product (generic ezetimibe) for 1 year if the patient meets one of the following criteria (A, B, C, D, E, F, G or H):
- **A)** Patient has tried one Step 1 Product; OR
- **B)** Generic ezetimibe is being initiated in combination with a Step 1 Product; OR
- **C)** Patient is taking or will be taking a medication that has a significant drug-drug interaction with a Step 1 Product; 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 Product (brand Zetia) for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient has tried the Step 2 Product (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 Product; OR
  - **ii.** Brand Zetia is being initiated in combination with a Step 1 Product; OR
  - **iii.** Patient is taking or will be taking a medication that has a significant drug-drug interaction with a Step 1 Product; 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
  - **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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6. Cabral BMI, Edding SN, Portocarrero JP, Lerma EV, et al. Rhabdomyolysis. *Dis Mon*. 2020;66(8):101015.
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8. Khattak ZE, Ashraf M. McArdle Disease. In: Stat Pearls [internet]. Treasure Island (FL): StatPearls Publishing; 2022 May 22.