STEP THERAPY POLICY

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

REVIEW DATE: 08/09/2023

OVERVIEW

Ezetimibe, an inhibitor of absorption of cholesterol by the small intestine, is indicated for:[1]

- **Primary hyperlipidemia**, including **heterozygous familial hypercholesterolemia (HeFH)**, **in adults**, in combination with a statin, or alone when additional low-density lipoprotein cholesterol (LDL-C) lowering therapy is not possible, as an adjunct to diet to reduce elevated LDL-C.
- **HeFH**, **in pediatric patients ≥ 10 years of age**, in combination with a statin as an adjunct to diet to reduce elevated LDL-C.
- **Mixed hyperlipidemia**, **in adults**, **in combination with fenofibrate** as an adjunct to diet to reduce elevated LDL-C.
- **Homozygous familial hypercholesterolemia (HoFH)**, **in adults and pediatric patients ≥ 10 years of age**, in combination with a statin and other LDL-C lowering therapies, to reduce elevated LDL-C levels.
- **Homozygous familial sitosterolemia**, **in adults and in pediatric patients ≥ 9 years of age**, as an adjunct to diet for the reduction of elevated sitosterol and campesterol levels.

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.[2-4,9,10] Ezetimibe can be used with statins for additive LDL-C 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.

- **The American College of Cardiology Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering** in the Management of Atherosclerotic cardiovascular disease (ASCVD) Risk (2022) make several recommendations regarding ezetimibe for patients at high risk based on the IMPROVE-IT trial.[9] Ezetimibe is recommended as the initial nonstatin therapy in patients with clinical ASCVD who are receiving maximally tolerated statin therapy and have an LDL-C level ≥ 70 mg/dL. In patients with clinical ASCVD who are judged to be at very high risk and are being considered for a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor antibody therapy, maximally tolerated LDL-C–lowering therapy should include maximally tolerated statin therapy and ezetimibe.
- **The American Heart Association and American College of Cardiology guidelines for the management of patients with chronic coronary disease** (2023) make several recommendations regarding ezetimibe. Statins remain first-line; however, ezetimibe has a role. In patients with chronic coronary disease who are considered to be at very high risk and on maximally tolerated statin therapy with an LDL-C ≥ 70 mg/dL, ezetimibe can be beneficial to further reduce the risk of major adverse cardiovascular events (MACE). In patients with chronic coronary disease who are not at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥ 70 mg/dL, it may be reasonable to add ezetimibe to further reduce the risk of MACE.

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] Statins are known teratogens whereas ezetimibe is more favorable in this regard.[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).[6-8]

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 is excluded from Step Therapy for 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 is excluded from Step Therapy forthe 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, Atorvaliq, 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 Zetia

CRITERIA

1. Approve the Step 2 Product (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 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 (A and B):
- **A)** Patient has tried the Step 2 Product (generic ezetimibe); AND
- **B)** Patient meets 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

1. Zetia® tablets [prescribing information]. Jersey City, NJ: Organon; July 2023.
2. Jellinger PS, Handelsman Y, Rosenblit PD. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. *Endocrine Pract*. 2017;23(Suppl 2):1-87.
3. Grundy SM, Stone NJ, Bailey AL, et al. ACC/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):e1046-e1081.
4. Newman CB, Blaha MJ, Boord JB, et al. Lipid management in patients with endocrine disorders: an Endocrinology Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2020;105(12):3613-3682.
5. Newman CB. Safety of statins and nonstatins for the treatment of dyslipidemia. *Endocrinol Metab Clin North Am*. 2022;51(3):655-679.
6. Cabral BMI, Edding SN, Portocarrero JP, Lerma EV, et al. Rhabdomyolysis. *Dis Mon*. 2020;66(8):101015.
7. Kodadek L, Carmichael SP, Seshadri A, et al. Rhabdomyolysis: an American Association for the Surgery of Trauma Critical Care Committee Clinical Consensus Document. *Trauma Surg Acute Care Open*. 2022;7:e000836.
8. Khattak ZE, Ashraf M. McArdle Disease. In: Stat Pearls [internet]. Treasure Island (FL): StatPearls Publishing; 2022 May 22.
9. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *J Am Coll Cardiol*. 2022;80(14):1366-1418.
10. Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2023 July 14. [Online ahead of print].