# Step Therapy
# Zetia® (ezetimibe tablets, generic)

## Table of Contents



## Product Identifier(s)

**Effective 1/1/23 to 2/27/23:** 108498

**Effective 2/28/23:** 12937

***INSTRUCTIONS FOR USE***
*The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.*

## National Formulary Medical Necessity

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.

**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

**Cigna covers Step 2 or 3 agents as medically necessary when the following criteria are met:**

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

2. Approve the Step 3 Product (brand Zetia) for 1 year if the individual meets the following criteria (A and B):
   - **A)** Individual has tried the Step 2 Product (generic ezetimibe); AND
   - **B)** Individual meet one of the following (i, ii, iii, iv, v, vi, vii or viii):
     - **i.** Individual has tried one Step 1 Product; OR
     - **ii.** Brand Zetia is being initiated in combination with a Step 1 Product; OR
     - **iii.** Individual is taking or will be taking a medication that has a significant drug-drug interaction with a Step 1 Product; OR
     - **iv.** Individual has severe renal impairment; OR
     - **v.** Individual has homozygous sitosterolemia (phytosterolemia); OR
     - **vi.** Individual is pregnant; OR
     - **vii.** Individual has active liver disease or unexplained persistent elevations of serum transaminases; OR
     - **viii.** Individual meets one of the following [(1) or (2)]:
       - **(1)** Individual has been previously diagnosed with myopathy or rhabdomyolysis (either medication-related or not medication-related); OR
       - **(2)** Individual has an underlying muscle/muscle-metabolism related disorder.

## Conditions Not Covered

Any other exception is considered not medically necessary.

## Background

**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]

## References


1. Zetia® tablets [prescribing information]. Jersey City, NJ: Organon; June 2021.
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. Available at: https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000625. Accessed on August 16, 2022.
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.


## Revision History

| Type of Revision | Summary of Changes | Approval Date |
|---|---|---|
| Annual Revision | No criteria changes. | 08/24/2022 |