Clinical Policy: Ezetimibe (Zetia)
Reference Number: CP.PMN.78
Effective Date: 02.01.17
Last Review Date: 02.19
Line of Business: Medicaid

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Ezetimibe (Zetia®) is an inhibitor of intestinal cholesterol (and related phytosterol) absorption.

FDA Approved Indication(s)
Zetia is indicated as an adjunct to diet to:
- 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 an 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 in patients with homozygous sitosterolemia (phytosterolemia)

Limitation(s) of use:
- The effect of Zetia on cardiovascular morbidity and mortality has not been determined.
- Zetia has not been studied in Fredrickson Type I, III, IV, and V dyslipidemias.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Zetia is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Hypercholesterolemia (must meet all):
      1. Diagnosis of hypercholesterolemia/hyperlipidemia;
      2. Age ≥ 10 years;
      3. Failure of a high intensity statin per Appendix B for ≥ 3 consecutive months unless one of the following applies (a, b, or c):
         a. Member has received a moderate intensity statin per Appendix B adherently for ≥ 3 consecutive months due to clinically significant adverse effects to high intensity statins;
b. Member has received a low intensity statin per Appendix B adherently ≥ 3 consecutive months due to clinically significant adverse effects to high and moderate intensity statins;
c. Statin therapy is contraindicated per Appendix D;
3. Member is adherent to statin therapy in the last 3 months as evidenced by pharmacy claims history, unless contraindicated;
4. Dose does not exceed 10 mg per day (1 tablet per day).

**Approval duration: 12 months**

B. **Sitosterolemia** (must meet all):
1. Diagnosis of homozygous sitosterolemia (phytosterolemia);
2. Age ≥ 10 years;
3. Dose does not exceed 10 mg per day (1 tablet per day).

**Approval duration: 12 months**

C. **Homozygous Familial Hypercholesterolemia, Heterozygous Familial Hypercholesterolemia, or Atherosclerotic Cardiovascular Disease** (must meet all):
1. Diagnosis of one of the following (a, b, or c):
   a. HoFH;
   b. Heterozygous familial hypercholesterolemia;
   c. Atherosclerotic cardiovascular disease;
2. Prescribed by or in consultation with a cardiologist, endocrinologist, or lipid specialist;
3. Age ≥ 10 years;
4. Dose does not exceed 10 mg per day (1 tablet per day).

**Approval duration: 12 months**

D. **Other diagnoses/indications**
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid.

II. **Continued Therapy**

A. **All Indications in Section I** (must meet all):
1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 10 mg per day (1 tablet per day).

**Approval duration: 12 months**

B. **Other diagnoses/indications** (must meet 1 or 2):
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.

**Approval duration: Duration of request or 12 months (whichever is less); or**
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:
A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information
Appendix A: Abbreviation/Acronym Key
Apo B: apolipoprotein B
FDA: Food and Drug Administration
HoFH: homozygous familial hypercholesterolemia
LDL-C: low-density lipoprotein cholesterol
non-HDL-C: non-high-density lipoprotein cholesterol
total-C: total cholesterol

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-Intensity Statin Therapy</strong></td>
<td>Daily dose shown to lower LDL-C, on average, by approximately ≥ 50%</td>
<td></td>
</tr>
<tr>
<td>atorvastatin (Lipitor®)</td>
<td>40-80 mg PO QD</td>
<td>80 mg/day</td>
</tr>
<tr>
<td>rosuvastatin (Crestor®)</td>
<td>20-40 mg PO QD</td>
<td>40 mg/day</td>
</tr>
<tr>
<td><strong>Moderate-Intensity Statin Therapy</strong></td>
<td>Daily dose shown to lower LDL-C, on average, by approximately 30% to &lt; 50%</td>
<td></td>
</tr>
<tr>
<td>atorvastatin (Lipitor®)</td>
<td>10-20 mg PO QD</td>
<td>80 mg/day</td>
</tr>
<tr>
<td>fluvastatin (Lescol XL®)</td>
<td>Regular release (generic only): 40 mg PO BID Extended release: 80 mg PO QD</td>
<td>80 mg/day</td>
</tr>
<tr>
<td>lovastatin</td>
<td>40 mg PO QD</td>
<td>80 mg/day</td>
</tr>
<tr>
<td>Livalo® (pitavastatin)</td>
<td>2-4 mg PO QD</td>
<td>4 mg/day</td>
</tr>
<tr>
<td>pravastatin (Pravachol®)</td>
<td>40-80 mg PO QD</td>
<td>80 mg/day</td>
</tr>
<tr>
<td>rosvastatin (Crestor®)</td>
<td>5-10 mg PO QD</td>
<td>40 mg/day</td>
</tr>
<tr>
<td>simvastatin (Zocor®)</td>
<td>20-40 mg PO QD</td>
<td>40 mg/day for most patients; 80 mg/day for patients already taking 80 mg/day chronically without evidence of myopathy</td>
</tr>
<tr>
<td><strong>Low-Intensity Statin Therapy</strong></td>
<td>Daily dose shown to lower LDL-C, on average, by &lt; 30%</td>
<td></td>
</tr>
<tr>
<td>fluvastatin</td>
<td>20-40 mg PO QD</td>
<td>80 mg/day</td>
</tr>
<tr>
<td>lovastatin</td>
<td>20 mg PO QD</td>
<td>80 mg/day</td>
</tr>
</tbody>
</table>
**Drug Name** | **Dosing Regimen** | **Dose Limit/Maximum Dose**
---|---|---
Livalo® (pitavastatin) | 1 mg PO QD | 4 mg/day
pravastatin (Pravachol®) | 10-20 mg PO QD | 80 mg/day
simvastatin (Zocor®) | 10 mg PO QD | 40 mg/day for most patients; 80 mg/day for patients already taking 80 mg/day chronically without evidence of myopathy

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

**Appendix C: Contraindications/Boxed Warnings**
- Contraindication(s):
  - Combination with a statin in patients with active liver disease or unexplained persistent elevations in hepatic transaminase levels
  - Women who are pregnant or may become pregnant
  - Nursing mothers
  - Patients with a known hypersensitivity to any component of this product
- Boxed warning(s): none reported

**Appendix D: Statin Contraindications**
- Decompensated liver disease (development of jaundice, ascites, variceal bleeding, encephalopathy)
- Laboratory-confirmed acute liver injury or rhabdomyolysis resulting from statin treatment
- Pregnancy, actively trying to become pregnant, or nursing
- Immune-mediated hypersensitivity to the HMG-CoA reductase inhibitor drug class (statins) as evidenced by an allergic reaction occurring with at least TWO different statins

**V. Dosage and Administration**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hyperlipidemia, HoFH, and homozygous sitosterolemia</td>
<td>10 mg PO QD</td>
<td>10 mg/day</td>
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**VI. Product Availability**

Tablets: 10 mg

**VII. References**
Ezetimibe


Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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<tr>
<td>01.17</td>
<td>02.17</td>
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New policy created
Policy split from CP.PMN.06 ezetimibe (Zetia) and ezetimibe and simvastatin (Vytorin) (retired) Clinical changes made to criteria:
New policy mandates the use of high intensity statin for 3 months and provides a pathway to approval for patients with familial hypercholesterolemia with involvement of a specialist.

1Q18 annual review: No significant changes; Age added per safety guidance endorsed by Centene Medical Affairs; Added “unless contraindicated” to requirement related to adherence to statin therapy; References reviewed and updated. 11.10.17 02.18

1Q 2019 annual review: no significant changes; references reviewed and updated. 12.12.18 02.19

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.
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This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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**Note: For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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