

Clinical Policy: Ezetimibe and Simvastatin (Vytorin)

Reference Number: CP.PMN.77

Effective Date: 02.01.17

Last Review Date: 02.19

Line of Business: Commercial, Medicaid

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

Ezetimibe/simvastatin (Vytorin[®]) contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and simvastatin, an HMG-CoA reductase inhibitor.

FDA Approved Indication(s)

Vytorin is indicated as adjunctive therapy to diet to:

- Reduce elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B, triglycerides, and non-high-density lipoprotein cholesterol, and to increase high-density lipoprotein cholesterol in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia
- Reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipid lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable

Limitation(s) of use:

- No incremental benefit of Vytorin on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.
- Vytorin 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 Vytorin 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 \geq 10 years;
3. Failure of a high intensity statin per Appendix B for \geq 3 consecutive months unless one of the following applies (a or b):
 - a. Member has used a moderate intensity statin per Appendix B adherently for \geq 3 consecutive months due to clinically significant adverse effects to high intensity statins;

- b. Member has used a low intensity statin per Appendix B adherently for ≥ 3 consecutive months due to clinically significant adverse effects to high and moderate intensity statins;
4. Adherence to statin therapy in the last 3 months as evidenced by pharmacy claims history;
5. Request does not exceed ezetimibe 10 mg/simvastatin 40 mg per day (1 tablet per day), or ezetimibe 10 mg/simvastatin 80 mg (1 tablet per day) for member on previous therapy with simvastatin 80 mg for at least one year.

Approval duration:

Medicaid – 12 months

Commercial – Length of Benefit

B. 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 (HeFH);
 - c. Atherosclerotic cardiovascular disease (ASCVD);
2. Prescribed by or in consultation with a cardiologist, endocrinologist, or lipid specialist;
3. Age ≥ 10 years;
4. Member is unable to use high intensity statins per Appendix B due to clinically significant adverse effects;
5. Request does not exceed ezetimibe 10 mg/simvastatin 40 mg per day (1 tablet per day), or ezetimibe 10 mg/simvastatin 80 mg (1 tablet per day) for member on previous therapy with simvastatin 80 mg for at least one year.

Approval duration:

Medicaid – 12 months

Commercial – Length of Benefit

C. 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.CPA.09 for commercial and 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 ezetimibe 10 mg/simvastatin 40 mg per day (1 tablet per day), or ezetimibe 10 mg/simvastatin 80 mg (1 tablet per day) for member on previous therapy with simvastatin 80 mg for at least one year.

Approval duration:

Medicaid – 12 months

Commercial – Length of Benefit

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.CPA.09 for commercial and 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.CPA.09 for commercial and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration

HoFH: homozygous familial hypercholesterolemia

LDL-C: low-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.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
High-Intensity Statin Therapy		
<i>Daily dose shown to lower LDL-C, on average, by approximately $\geq 50\%$</i>		
atorvastatin (Lipitor [®])	40-80 mg PO QD	80 mg/day
rosuvastatin (Crestor [®])	20-40 mg PO QD	40 mg/day
Moderate-Intensity Statin Therapy		
<i>Daily dose shown to lower LDL-C, on average, by approximately 30% to < 50%</i>		
atorvastatin (Lipitor [®])	10-20mg PO QD	80 mg/day
fluvastatin (Lescol XL [®])	Regular-release (generic only): 40 mg PO BID Extended-release: 80 mg PO QD	80 mg/day
lovastatin	40 mg PO QD	80 mg/day
Livalo [®] (pitavastatin)	2-4 mg PO QD	4 mg/day
pravastatin (Pravachol [®])	40-80 mg PO QD	80 mg/day
rosuvastatin (Crestor [®])	5-10 mg PO QD	40 mg/day
simvastatin (Zocor [®])	20-40 mg PO QD	40 mg/day for most patients; 80 mg/day for patients already taking 80

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
		mg/day chronically without evidence of myopathy
Low-Intensity Statin Therapy		
<i>Daily dose shown to lower LDL-C, on average, by < 30%</i>		
fluvastatin	20-40 mg PO QD	80 mg/day
lovastatin	20 mg PO QD	80 mg/day
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):
 - Concomitant administration of strong CYP3A4 inhibitors.
 - Concomitant administration of gemfibrozil, cyclosporine, or danazol.
 - Hypersensitivity to any component of this medication.
 - Active liver disease or unexplained persistent elevations of hepatic transaminase levels
 - Women who are pregnant or may become pregnant
 - Nursing mothers
- Boxed warning(s): none reported

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Primary hyperlipidemia and HoFH	<p>Usual: 10/10 mg/day to 10/40 mg/day</p> <p>Use of the 10/80-mg dose of Vytorin should be restricted to patients who have been taking Vytorin 10/80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity.</p> <p>Due to the increased risk of myopathy, including rhabdomyolysis, associated with the 10/80-mg dose of Vytorin, patients unable to achieve their LDL-C goal utilizing the 10/40-mg dose of Vytorin should not be titrated to the 10/80-mg dose, but should be placed on alternative LDL-C-lowering treatment(s) that provides greater LDL-C lowering.</p>	<p>10/40 mg/day for most patients</p> <p>10/80 mg/day for patients already taking simvastatin 80 mg/day chronically without evidence of myopathy</p>

VI. Product Availability

Tablets (ezetimibe mg/simvastatin mg): 10/10, 10/20, 10/40, 10/80

VII. References

1. Vytorin Prescribing Information. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; February 2018. Available at: www.vytorin.com/hcp.xhtml. Accessed November 13, 2018.
2. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2016;68:92–125.
3. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. *Endocr Pract.* 2017 Apr;23(Suppl 2):1-87.
4. Third Report of the National Cholesterol Educational Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). <https://www.nhlbi.nih.gov/files/docs/guidelines/atp3xsum.pdf>. Accessed December 1, 2016.
5. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014; 129: S1.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
<p>New policy created. Policy split from CP.PMN.06 ezetimibe (Zetia) and ezetimibe and simvastatin (Vytorin) (retired) New policy mandates the use of high intensity statin for 3 months and provides a pathway to approval for patients with familial hypercholesterolemia & ASCVD with involvement of a specialist. Requirement for use of a high intensity statin is maintained unless contraindicated as Vytorin can only be initiated at moderate intensity. In prior policy, members who claim to have contraindication to statin are able to obtain this medication; this new policy corrects this.</p>	01.17	02.17
<p>1Q18 annual review: Policies combined for Centene Medicaid and Commercial lines of business [CP.CPA.62 Pitavastatin (Livalo), Ezetimibe/Simvastatin (Vytorin 10/10 mg) and CP.CPA.169 (Vytorin 10/80 mg)]. Retired Livalo from CP.CPA.62 (previously combined with Vytorin 10/10)-refer to CP.CPA.190 Formulary Exceptions policy; No significant changes from previous corporate approved policy; Age added per safety guidance endorsed by</p>	11.14.17	02.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Centene Medical Affairs; Commercial: removed “One of the following (a or b): a. Failure to achieve NCEP goals; b. Failure of one generic formulary statin unless contraindicated or clinically significant adverse effects are experienced” and replaced it with the use of high-, moderate-, or low-intensity statin for 3 months; added adherence to statin therapy as a requirement; updated policy provides a pathway to approval for patients with HeFH and ASCVD with involvement of a specialist; Medicaid: for HoFH, HeFH, ASCVD, and re-auth- updated to allow use of the 10/80-mg dose of Vytorin in patients who have been taking simvastatin 80 mg for 12 months or more; References reviewed and updated.		
1Q 2019 annual review: no significant changes; references reviewed and updated.	11.20.18	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.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

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.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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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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