Clinical Policy Title:	bempedoic acid; bempedoic acid and ezetimibe
Policy Number:	RxA.651
Drug(s) Applied:	Nexletol™/Nexlizet™
Original Policy Date:	09/14/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

Bempedoic acid (Nexletol™)/ bempedoic acid and ezetimibe (Nexlizet™) both contains adenosine triphosphate-citrate lyase (ACL) inhibitor,w Nexletol™ contains a cholesterol absorption indicator as well. They are both indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C.

Limitations of Use: The effect on cardiovascular morbidity and mortality has not been determined.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
bempedoic acid (Nexletol™)	HeFH or established ASCVD who require additional lowering of LDL-C.	180 mg once daily	180 mg/day orally bempedoic acid
bempedoic acid and ezetimibe (Nexlizet™)	HeFH or established ASCVD who require additional lowering of LDL-C.	180 mg bempedoic acid and 10 mg ezetimibe orally once daily with or without food	180 mg/day orally bempedoic acid and 10 mg/day orally ezetimibe

Dosage Forms

- Tablet: Nexletol™: 180 mg bempedoic acid; Nexlizet™: 180 mg of bempedoic acid/10 mg of ezetimibe.

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Heterozygous familial hypercholesterolemia (must meet all):

1. Diagnosis of HeFH;
2. Age ≥ 18 years
3. Prescribed by or in consultation with a cardiologist, endocrinologist or lipidologist;;
4. Member meets one of the following (a or b):
   a. Is on concomitant statin therapy at the maximum tolerated dose;
   b. Individual is statin intolerant based on one of the following (i or ii):
      i. Inability to tolerate at least two statins, with at least one started at the lowest starting daily dose, demonstrated by intolerable symptoms or clinically significant biomarker changes; or statin associated rhabdomyolysis after a trial of one statin;
      ii. Has a contraindication for statin therapy including active liver disease, unexplained persistent elevation of hepatic transaminases or pregnancy.
5. Request meets one of the following (a or b):
   a. If the request is for Nexletol™, dose does not exceed: 180 mg bempedoic acid;
   b. If the request is for Nexlizet™, dose does not exceed: 180 mg of bempedoic acid/10 mg of ezetimibe.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

B. Established ASCVD who require additional lowering of LDL-C (must meet all):

1. Diagnosis of ASCVD;
2. Age ≥ 18 years;
3. Prescribed by or in consultation with a cardiologist, endocrinologist or lipidologist;;
4. Individual has a history of clinical atherosclerotic cardiovascular disease (ASCVD), including one or more of the following:
   a. Acute coronary syndrome;
   b. Coronary artery disease (CAD);
   c. History of myocardial infarction (MI);
   d. Stable or unstable angina;
   e. Coronary or other arterial revascularization;
   f. Stroke;
   g. Transient ischemic attack (TIA);
   h. Peripheral arterial disease (PAD)
6. Member meets one of the following (a or b);
   a. Is on concomitant statin therapy at the maximum tolerated dose;
   b. Individual is statin intolerant based on one of the following (i or ii):
      i. Inability to tolerate at least two statins, with at least one started at the lowest starting daily dose, demonstrated by intolerable symptoms or clinically significant biomarker changes; or statin associated rhabdomyolysis after a trial of one statin;
      ii. Has a contraindication for statin therapy including active liver disease, unexplained persistent elevation of hepatic transaminases or pregnancy.
7. Request meets one of the following (a or b):
   a. If the request is for Nexletol™, dose does not exceed: 180 mg bempedoic acid;
   b. If the request is for Nexlizet™, dose does not exceed: 180 mg of bempedoic acid/10 mg of ezetimibe.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy (lab results showing LDL-C reduction since initiation of therapy);
3. If statin tolerant, documentation of adherence to a statin at the maximally tolerated dose;
4. Request meets one of the following (a or b):
   a. If the request is for Nexletol™, dose does not exceed: 180 mg bempedoic acid;
   b. If the request is for Nexlizet™, dose does not exceed: 180 mg of bempedoic acid/10 mg of ezetimibe.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
ACL: adenosine triphosphate-citrate lyase
ASCVD: atherosclerotic cardiovascular disease
HeFH: Heterozygous familial hypercholesterolemia

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
atorvastatin (Lipitor®)	10 mg/day; the usual dose range is 10 to 20 mg orally once daily in patients requiring greater than 45% LDL-reduction. The dosage range is 10 to 80 mg orally once daily (mean LDL reduction range: 43% to 60% LDL). 80 mg orally once daily has been shown to reduce the progression of atherosclerosis in clinical trials.	80 mg/day orally
fluvastatin (Lescol XL ®)	20 to 40 mg orally once daily (22% to 25% LDL reduction), titrated up to 40 mg orally twice daily (or switch to extended release Fluvastatin 80 mg orally once daily) to achieve 35% to 36% LDL reduction. In patients with coronary heart disease, Fluvastatin 40 mg orally twice daily.	80 mg/day orally
lovastatin (Altoprev ®)	Initially, 10 to 20 mg orally once daily with the evening meal. Patients requiring LDL reductions of 20% or more to achieve their goal may begin with 20 mg orally once daily, while patients requiring lower reductions may begin with 10 mg orally once daily. Initially, 20 mg orally once daily with the evening meal. The recommended dosing range is 10 to 80 mg/day orally in single or two divided doses for slowing the progression of coronary atherosclerosis.	80 mg/day orally

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

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Known hypersensitivity to ezetimibe tablets.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

- Hyperuricemia: Elevations in serum uric acid have occurred. Assess uric acid levels periodically as clinically indicated. Monitor for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate.
- Tendon Rupture: Tendon rupture has occurred. Discontinue Nexletol™ at the first sign of tendon rupture. Avoid Nexletol™ in patients who have a history of tendon disorders or tendon rupture.

References

1. Nexletol™ (bempedoic acid) [prescribing information]. Ann Arbor, MI: Esperion Therapeutics, Inc. February 2020. Available at: https://pi.esperion.com/nexletol/nexletol-pi.pdf. Accessed on July 09, 2021.
2. Nexlizet™ (bempedoic acid and ezetimibe) [prescribing information]. Ann Arbor, MI: Esperion Therapeutics, Inc. November 2020. Available at: https://pi.esperion.com/nexlizet/nexlizet-pi.pdf. Accessed on July 09, 2021.
3. Grundy SM, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. Journal of the American College of Cardiology. 2019; 73(24): e285-e350. doi: doi.org/10.1016/j.jacc.2018.11.003. Available at: https://pubmed.ncbi.nlm.nih.gov/30423393/. Accessed on July 09, 2021.
4. Jacobson TA, et al. National Lipid Association recommendations for patient-centred management of dyslipidemia: part 1 – full report. Journal of Clinical Lipidology. March 2015; 9(2): 129-169. http://dx.doi.org/10.1016/j.jacl.2015.02.003. Accessed on July 09, 2021.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	08/27/2020	09/14/2020
Policy was reviewed: 1) Clinical Policy Title was updated to include "bempedoic acid and ezetimibe". 2) Background was updated from "NEXLETOL/NEXLIZET is an adenosine triphosphate-citrate lyase (ACL) inhibitor indicated as an adjunct to diet and maximally tolerated	07/09/2021	09/14/2021

statin therapy for the treatment of adults with heterozygous…" to "Bempedoic acid (Nexletol™)/ bempedoic acid and ezetimibe (Nexlizet™) both contains adenosine triphosphate-citrate lyase (ACL) inhibitor,w Nexletol™ contains a cholesterol absorption…". 3) Background was updated to include Limitations of Use, "Limitations of Use: The effect on cardiovascular morbidity and mortality has not been determined.". 4) Dosing Information indication for Nexletol was updated to remove "Indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with". 5) Dosing Information indication for Nexlizet was updated to remove "Indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with". 6) Dosing Information dosing regimen for Nexlizet was updated from "180 mg once daily and 10 mg/day PO ezetimibe" to "180 mg bempedoic acid and 10 mg ezetimibe orally once daily with or without food". 7) Dosing Information maximum dose for Nexlizet was updated from "bempedoic acid: 180 mg once daily" to "180 mg/day		

orally bempedoic acid and 10 mg/day orally ezetimibe”. 8) Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 9) Initial Approval Criteria I.A.3 was updated to include prescriber criteria, “Prescribed by or in consultation with a cardiologist, endocrinologist or lipidologist;”. 10) Initial Approval Criteria I.A.5 was updated to include “Request meets one of the following (a or b)…”. 11) Initial Approval Criteria I.A.5.a was updated to include “If the request is for Nexletol™, dose does not exceed: 180 mg bempedoic acid;”. 12) Initial Approval Criteria I.A.5.b was updated to include “If the request is for Nexlizet™, dose does not exceed: 180 mg of bempedoic acid/10 mg of ezetimibe.”. 13) Initial Approval Criteria I.B.1 was updated to include “Diagnosis of ASCVD;”. 14) Initial Approval Criteria I.B.2 was updated to include age criteria, “Age ≥ 18 years;”. 15) Initial Approval Criteria I.B.3 was updated to include prescriber criteria, “Prescribed by or in consultation with a cardiologist, endocrinologist or lipidologist;”.		

16) Initial Approval Criteria I.B.7 was updated to include “Request meets one of the following (a or b)…”. 17) Initial Approval Criteria I.B.7.a was updated to include “If the request is for Nexletol™, dose does not exceed: 180 mg bempedoic acid;”. 18) Initial Approval Criteria I.B.7.b was updated to include “If the request is for Nexlizet™, dose does not exceed: 180 mg of bempedoic acid/10 mg of ezetimibe.”. 19) Continued Therapy Approval Criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 20) Continued Therapy Approval Criteria II.A.2 was updated to include “…(lab results showing LDL-C reduction since initiation of therapy);”. 21) Continued Therapy Approval Criteria II.A.3 was updated from “Member continues to receive concomitant maximally tolerated statin therapy” to “If statin tolerant, documentation of adherence to a statin at the maximally tolerated dose;”. 22) Continued Therapy Approval Criteria II.A.4 was updated to include “Request meets one of the following (a or b)…”. 23) Continued Therapy Approval Criteria II.A.4.a was updated to include “If the request is		

for Nexletol™, dose does not exceed: 180 mg bempedoic acid;”. 24) Continued Therapy Approval Criteria II.A.4.b was updated to include “If the request is for Nexlizet™, dose does not exceed: 180 mg of bempedoic acid/10 mg of ezetimibe.”. 25) Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance..". 26) Appendix B was updated to include alternate drugs atorvastatin (Lipitor®), fluvastatin (Lescol XL ®), and lovastatin (Altoprev ®), in addition to their specific dosing regimens and maximum doses. 27) Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 28) Appendix C was updated to include contraindication, “Known hypersensitivity to ezetimibe tablets.”. 29) Appendix D was updated to include warnings and precautions, “Hyperuricemia: Elevations in serum uric acid have occurred…” and		

"Tendon Rupture: Tendon rupture has occurred…" 30) References were reviewed and updated.		