BlueCross BlueShield of Kansas
An Independent Licensee of the Blue Cross and Blue Shield Association.

Bempedoic Acid Prior Authorization with Quantity Limit Program Summary

FDA APPROVED INDICATIONS AND DOSAGE[1,2]

Agent(s)	Indication(s)	Dosage
Nexletol™ (bempedoic acid) Tablet	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. Limitation of Use: The effect of bempedoic acid on cardiovascular morbidity and mortality has not been determined.	The recommended dosage in combination with maximally tolerated statin therapy, is 180 mg administered orally once daily.
Nexlizet™ (bempedoic acid/ ezetimibe) Tablet	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. Limitation of Use: The effect of bempedoic acid on cardiovascular morbidity and mortality has not been determined.	The recommended dosage in combination with maximally tolerated statin therapy, is one tablet orally once daily. One tablet contains 180 mg of bempedoic acid and 10 mg of ezetimibe. After initiation, analyze lipid levels within 8 to 12 weeks

CLINICAL RATIONALE

Familial hypercholesterolemia (FH) is a common yet underdiagnosed autosomal dominant disorder that affects 1 in 220 individuals globally. An individual who is heterozygous for FH (HeFH) has a 50% chance of passing the gene to his or her children. FH is characterized by lifelong elevation of low-density lipoprotein cholesterol (LDL-C) and, if untreated, leads to early-onset atherosclerosis and increased risk of cardiovascular events. Affected men and women who are untreated have a 30% to 50% risk of a fatal or nonfatal cardiac event by ages 50 and 60 years, respectively. FH is generally a silent disease. Given the broad range of causes of hypercholesterolemia and early-onset coronary artery disease (CAD), it is not surprising that FH is not always in the differential diagnosis for healthcare professionals when confronted with a patient presenting with early CAD. Although diagnosis can be made on the basis of clinical features, genetic testing may offer additional insight regarding cardiac risk and diagnosis. There are no internationally agreed-upon criteria for the diagnosis of FH, so useful diagnostic criteria have been developed. Two of the criteria, the UK Simon Broome system and the Dutch Lipid Clinic Network criteria incorporate genetic tests into their algorithm.

Heterozygous familial hypercholesterolemia (HeFH)
The Simon Broome Register criteria and Dutch Lipid clinic Network criteria have been developed to aid in diagnosing HeFH.[5] Definitive diagnosis of HeFH according to Simon Broome diagnostic criteria requires the patient has one of the following:[4,5]

- Total cholesterol greater than 6.7 mmol/L or low-density lipoprotein cholesterol (LDL-C) greater than 4.0 mmol/L in a child aged younger than 16 years, or greater than 7.5 mmol/L or LDL-C greater than 4.9 mmol/L in an adult (levels either pre-treatment or highest on treatment) **plus** tendon xanthomas in the patient, or in first-degree relative (parent, sibling or child), or in second-degree relative (e.g. grandparent, uncle or aunt)
- DNA-based evidence of an LDL receptor mutation, familial defective Apo B-100, or a PCSK9 mutation

The Dutch Lipid Clinic Network criteria assign points based on cholesterol levels, family history of hyperlipidemia or cardiovascular disease, clinical presentation, and/or presence of identified genetic mutation affecting plasma LDL-C.[5-7] A definitive diagnosis of HeFH can be made in patients with greater than 8 points.

Dutch Lipid Clinic Network criteria for diagnosis of heterozygous familial hypercholesterolemia.[8]

Group 1: Family history	**Points**
• First-degree relative with known premature (<55 years, men; <60 years, women) coronary heart disease (CHD)	1
• First-degree relative with known LDL cholesterol >95th percentile by age and gender for country	1
• First-degree relative with tendon xanthoma and/or corneal arcus	2
• Children <18 years with LDL cholesterol >95th percentile by age and gender for country	2
Group 2: Clinical history	**Points**
• Subject has premature (<55 years, men; <60 years, women) CHD	2
• Subject has premature (<55 years, men; <60 years, women) cerebral or peripheral vascular disease	1
Group 3: Physical examination	**Points**
• Tendon xanthoma	6
• Corneal arcus in a person <45 years	4
Group 4: Biochemical results (LDL-C)	**Points**
• >8.5 mmol/L (>325 mg/dL)	8
• 6.5–8.4 mmol/L (251–325 mg/dL)	5
• 5.0–6.4 mmol/L (191–250 mg/dL)	3
• 4.0–4.9 mmol/L (155–190 mg/dL)	1
Group 5: Molecular genetic testing (DNA analysis)	**Points**
• Causative mutation shown in the LDLR, APOB, or PCSK9 genes	8
Use and Interpretation	
Assign only one score, the highest applicable, per group then add the points from each group to achieve the total score Definitive FH diagnosis: > 8 points Probable FH diagnosis: 6 to 8 points Possible FH diagnosis: 3 to 5 points Unlikely FH diagnosis: 0 to 2 points	

Atherosclerotic Cardiovascular Disease (ASCVD) – Secondary Prevention

The AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline lists the following as clinical ASCVD:[9]

- Acute coronary syndrome (ACS)
- Myocardial infarction (MI)
- Stable or unstable angina or coronary or other arterial revascularization
- Stroke
- Transient ischemic attack (TIA) or peripheral artery disease (PAD) including aortic aneurysm

Safety

Nexletol has no contraindication or black box warnings.[1]

Nexlizet has no black box warnings, but has the following contraindication:[2]

- Known hypersensitivity to ezetimibe tablets

REFERENCES

1. Nexletol prescribing information. Esperion Therapeutics, Inc. February 2020.
2. Nexlizet prescribing information. Esperion Therapeutics, Inc. November 2020.
3. McGowan MP, Dehkordi SH, Moriarty PM, et. Al. "Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia". JAHA 8 (24) 2019. Available at: https://www.ahajournals.org/doi/10.1161/JAHA.119.013225 Accessed 4/29/2021
4. Identification and Management of Familial Hypercholesterolemia. Simon Broome Diagnostic criteria for index individuals and relatives. Available at: http://www.ncbi.nlm.nih.gov/books/NBK53810/ Accessed 4/29/2021
5. National Collaborating Centre for Primary Care (UK). Identification and Management of Familial Hypercholesterolaemia (FH) [Internet]. London: Royal College of General Practitioners (UK); 2008 Aug. (NICE Clinical Guidelines, No. 71.) 3, Diagnosis. Available from: https://www.nice.org.uk/guidance/CG71 Accessed 4/29/2021.
6. World Health Organization. Familial Hypercholesterolaemia (FH): Report of a second WHO consultation. Geneva: World Health Organization; 1999 Available at: https://apps.who.int/iris/handle/10665/66346 Accessed 4/29/2021.
7. Nordestgaard BG, Chapman MJ, Humphries ST, et al; for the European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. *Eur Heart J*. 2013. doi.10.1093/eurheartj/eht273. https://pubmed.ncbi.nlm.nih.gov/23956253/ Accessed 4/29/2021.
8. Gidding S, Champagne M, Ferranti S, et al. The Agenda for Familial Hypercholesterolemia. A Scientific Statement From the American Heart Association. *Circulation*. 2015; 132:00-00 https://www.ahajournals.org/doi/10.1161/CIR.0000000000000297 Accessed 4/29/2021
9. 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. https://www.ahajournals.org/doi/10.1161/CIR.0000000000000625 Accessed 4/29/2021

Bempedoic Acid Prior Authorization with Quantity Limit

TARGET AGENT(S)
Nexletol™ (bempedoic acid)
Nexlizet™ (bempedoic acid/ezetimibe)

Brand (generic)	GPI	Multisource Code	Quantity Limit (per day or as listed)
Nexletol (bempedoic acid)			
180 mg tablet	39380020000320	M, N, O, or Y	1 tablet
Nexlizet (bempedoic acid/ezetimibe)			
180 mg / 10 mg tablet	39991002200320	M, N, O, or Y	1 tablet

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
    A. BOTH of the following:
        i. The patient has ONE of the following:
            1. A diagnosis of heterozygous familial hypercholesterolemia (HeFH) confirmed by ONE of the following:
                a. Genetic confirmation of <u>one</u> mutant allele at the *LDLR, Apo-B, PCSK9*, or *ARH* adaptor protein *1/LDLRAP1* gene locus
                OR
                b. BOTH of the following:
                    i. ONE of the following:
                        1. History of total cholesterol >290 mg/dL (>7.5 mmol/L) (pretreatment or highest level while on treatment)
                        OR
                        2. History of LDL-C >190 mg/dL (>4.9 mmol/L) (pretreatment or highest level while on treatment)
                    AND
                    ii. History of tendon xanthomas in ONE of the following:
                        1. The patient
                        OR
                        2. The patient's first degree relative (i.e. parent, sibling, or child)
                        OR
                        3. The patient's second degree relative (e.g. grandparent, uncle, or aunt)
                OR
                c. The Patient has a Dutch Lipid Clinic Network Criteria score of greater than 5
            OR
            2. A diagnosis of clinical atherosclerotic cardiovascular disease (ASCVD) defined as having ONE of the following:
                a. Acute coronary syndrome

b. History of myocardial infarction
c. Stable or unstable angina
d. Coronary or other arterial revascularization
e. Stroke
f. Transient ischemic attack
g. Peripheral arterial disease, including aortic aneurysm, presumed to be of atherosclerotic origin

AND

ii. ONE of the following:
1. The patient is on maximally tolerated statin therapy
OR
2. The patient has an intolerance or has a hypersensitivity to statin therapy
OR
3. The patient has an FDA labeled contraindication to ALL statins

OR

B. The patient has another FDA approved indication for the requested agent and route of administration
OR
C. The patient has another indication that is supported in compendia for the requested agent and route of administration

AND

2. ONE of the following:
A. The patient's age is within FDA labeling for the requested indication for the requested agent
OR
B. The prescriber has provided information in support of using the requested agent for the patient's age

AND

3. The patient does NOT have any FDA labeled contraindications to the requested agent

AND

4. ONE of the following:
A. The requested quantity (dose) does NOT exceed the program quantity limit
OR
B. ALL of the following:
i. The requested quantity (dose) is greater than the program quantity limit
AND
ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication
AND
iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

OR

C. ALL of the following:
i. The requested quantity (dose) is greater than the program quantity limit
AND
ii. The requested quantity (dose) is greater than the maximum FDA labeled dose for the requested indication
AND
iii. The prescriber has provided information in support of therapy with a

higher dose for the requested indication

Compendia Allowed: AHFS, or DrugDex 1 or 2a level of evidence

Length of Approval: 12 months

Renewal Evaluation

Target Agent(s) will be approved for renewal when ALL of the following criteria are met:

1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process
   AND
2. The patient has had clinical benefit with the requested agent
   AND
3. If the patient has ASCVD or HeFH, then ONE of the following:
   A. The patient is on maximally tolerated statin therapy
      OR
   B. The patient has an intolerance or hypersensitivity to statin therapy
      OR
   C. The patient has an FDA labeled contraindication to ALL statins
   AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
5. ONE of the following:
   A. The requested quantity (dose) does NOT exceed the program quantity limit
      OR
   B. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
         AND
      ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication
         AND
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit
   OR
   C. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
         AND
      ii. The requested quantity (dose) is greater than the maximum FDA labeled dose for the requested indication
         AND
      iii. The prescriber has provided information in support of therapy with a higher dose for the requested indication

Length of Approval: 12 months