Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

Effective Date: 04/08/2021

Evkeeza™ (evinacumab-dgnb)

FDA approval: February 11, 2021
HCPCS: J3590
Benefit: Medical

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved indication
   b. FDA approved age
   c. Trial and therapeutic failure of one high-intensity statin
      OR
   d. History of statin-associated side effects or intolerance (e.g., skeletal muscle related symptoms) after a trial of two generic statins
      OR
   e. History of rhabdomyolysis after a trial of one statin
   f. Trial and failure, contraindication or intolerance to a preferred PCSK9 inhibitor approved for use in homozygous familial hypercholesterolemia
   g. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list.

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limit: Align with FDA recommended dosing
   b. Authorization Period: One year at a time
   c. Renewal Criteria: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit.

***Note: Coverage may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

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Therapeutic considerations:

A. **FDA approved indication / Diagnosis**

**Please refer to most recent prescribing information.*

B. **Background Information**

a. Homozygous familial hypercholesterolemia (HoFH) is an ultra-rare inherited disease affecting approximately 1,300 patients in the United States. Patients with HoFH have mutations in the LDL receptor that result in virtually absent or impaired receptor-mediated catabolism of LDL cholesterol (LDL-C), leading to severely elevated LDL-C levels (> 400 mg/dL) and a lack of responsiveness to standard lipid-lowering therapies. Persistently elevated LDL-C increases the risk of premature atherosclerotic cardiovascular disease (ASCVD) and cardiac events in HoFH patients, often manifesting as early as the teenage years.

b. HoFH can be diagnosed via genetic testing for causative mutations in the *LDLR*, *APOB*, and *PCSK9* genes, with *LDLR* mutations being the most common. Clinical diagnosis of HoFH can also be made in patients with an untreated LDL-C > 500 mg/dL or treated LDL-C $\geq$ 300 mg/dL, plus one of the following: cutaneous or tendon xanthoma prior to 10 years of age, or elevated LDL-C levels in both parents consistent with heterozygous familial hypercholesterolemia (HeFH). Of note, untreated LDL-C < 500 mg/dL may be present in some patients with HoFH; this may particularly be the case in young children and would warrant consideration of genetic testing to confirm or clarify the diagnosis.

c. In their 2018 guideline on the management of blood cholesterol, the American College of Cardiology (ACC) and American Heart Association (AHA) task force on clinical practice guidelines recommends treatment with high intensity or maximally tolerated statin therapy for adult patients with LDL-C levels $\geq$ 190 mg/dL due to the increased risk of atherosclerotic cardiovascular disease (ASCVD) and both premature and recurrent coronary events. High intensity statins (atorvastatin 40 mg – 80 mg and rosuvastatin 20 mg – 40 mg) are expected to lower LDL-C by at least 50% and in clinical trials have been shown to provide greater ASCVD risk reduction than moderate intensity statins or placebo.

d. If with a high-intensity statin the patient experiences statin-associated side effects that are not severe (e.g., myalgias), the statin dose can be reduced or alternate statins can be trialed with the ultimate goal of treating with a guideline-recommended maximally tolerated statin. There are a variety of generically available statins that can be dosed at different intensities or dosing regimens to help mitigate bothersome side effects; therefore, it is reasonable to require a trial of at least two statins in patients experiencing statin-associated side effects. Patients who experience more severe side effects with statin therapy (e.g. rhabdomyolysis) or recurrent statin-associated muscle symptoms despite multiple statin rechallenge attempts may need to discontinue statin use and transition to non-statin therapy that has been shown to provide clinical benefit.

e. If maximally tolerated statin therapy fails to reduce LDL-C by at least 50% and/or the LDL-C level remains $\geq$ 100 mg/dL, the guideline suggests that additional ASCVD risk reduction can be derived from the addition of ezetimibe to statin therapy. Should LDL-C remain $\geq$ 100 mg/dL despite treatment with a maximally tolerated statin and ezetimibe, addition of a PCSK9 inhibitor may be considered; currently Repatha (evolocumab) is the only PCSK9 inhibitor approved for the treatment of HoFH. For persistent severe hypercholesterolemia where drug therapy fails to adequately control LDL-C, LDL apheresis may be an option and referral to a lipid specialist may be indicated.

f. For children and adolescents 10 years of age and older with an LDL-C $\geq$ 190 mg/dL or $\geq$ 160 mg/dL with a clinical presentation consistent with familial hypercholesterolemia who do not respond adequately to 3 to 6 months of lifestyle therapy, the 2018 guidelines suggest initiation of statin therapy. Statin treatment intensity

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in children is not specified in the guidelines as it should be individualized to the child based on the severity of hypercholesterolemia and the needs of the child/family.

g. Use of non-statin therapies to further treat HoFH in children is not addressed in the guidelines; however, since Repatha is approved by the FDA for use in pediatric patients 13 years of age and older with HoFH in combination with diet and other LDL-C lowering therapies, it is a reasonable next step for children and adolescents who require additional LDL-C lowering.

h. Evkeeza (evinacumab-dgnb) is a novel therapy for the treatment of HoFH, approved as an adjunct to other LDL-C-lowering therapies for both adults and pediatric patients 12 years of age and older. It is the first FDA-approved treatment that binds to and blocks angiopoietin-like 3 (ANGPTL3), a protein that aids in lipid metabolism. Due to the mutations affecting LDL receptor function, patients with HoFH are often less responsive or unresponsive to standard lipid-lowering therapies (e.g. statins, PCSK9 inhibitors) whose mechanism of action largely depend on up-regulating LDL receptor function. By inhibiting ANGPTL3, Evkeeza is able to significantly reduce LDL-C levels independent of LDL receptor function.

i. The Phase III ELIPSE HoFH trial demonstrated that Evkeeza, when taken in addition to other lipid-lowering therapies (including maximally tolerated statins, PCSK9 inhibitors, ezetimibe, lomitapide, and LDL apheresis), reduced LDL-C by a statistically significant 49% after 24 weeks compared to a 2% increase with lipid-lowering therapies alone (placebo) in patients with HoFH. Similar LDL-C lowering effects were observed in even the most difficult-to-treat patients who were unresponsive to other therapies due to limited or absent LDL receptor function.

j. Of note, the safety and efficacy of Evkeeza have not been established in patients with other causes of hypercholesterolemia, including heterozygous familial hypercholesterolemia (HeFH). Additionally, the effects of Evkeeza on cardiovascular morbidity and mortality have not yet been determined; however, it has been established that lowering LDL-C confers a lowered cardiovascular risk that is proportional to the reduction in LDL-C levels.

C. **Efficacy**

**Please refer to most recent prescribing information.*

D. **Medication Safety Considerations**

**Please refer to most recent prescribing information.*

E. **Dosing and administration**

**Please refer to most recent prescribing information.*

F. **How supplied**

**Please refer to most recent prescribing information.*

References:

1. Evkeeza [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals Inc; February 2021.
2. Repatha [prescribing information]. Thousand Oaks, CA: Amgen Inc; May 2020.
3. Bouhairie VE and Goldberg AC. Familial Hypercholesterolemia. Cardiol Clin. 2015 May; 33(2): 169-179. doi: 10.1016/j.ccl.2015.01.001.

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4. Raal FJ et al. Evinacumab for Homozygous Familial Hypercholesterolemia. N Engl J Med 2020; 383: 711-20.
5. Raal FJ et al. Familial hypercholesterolemia treatments: Guidelines and new therapies. Atherosclerosis 277 (2018) 483-492.
6. Lloyd-Jones et al. 2017 Focused Update of the 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. JACC Vol. 70. No. 14. 2017: 1785-822.
7. Grundy SM, et al. 2018 AHA/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. JACC Vol. 73, No. 24. 2019: e285-e350. https://doi.org/10.1016/j.jacc.2018.11.003.
8. De Ferranti SD. Familial hypercholesterolemia in children. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2021.
9. Rosenson RS and Durrington P. Familial hypercholesterolemia in adults: Overview. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2021.
10. Rosenson RS and Durrington P. Familial hypercholesterolemia in adults: Treatment. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2021.

<table>
<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>1.4</td><td>Effective Date: 06/22/2021</td><td>Add PA to BCNA and MAPPO
<table><tr><th>Line of Business</th><th>PA Required (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>Yes</td></tr><tr><td>BCNA</td><td>Yes</td></tr></table></td></tr>
<tr><td>1.3</td><td>Effective Date: 05/03/2021</td><td>Add PA to BCBSM
<table><tr><th>Line of Business</th><th>PA Required (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>No</td></tr><tr><td>BCNA</td><td>No</td></tr></table></td></tr>
<tr><td>1.2</td><td>Effective Date: 04/08/2021</td><td>New Policy</td></tr>
<tr><td>1.1</td><td>Effective Date: 04/05/2021</td><td>Add PA to BCN
<table><tr><th>Line of Business</th><th>PA Required (Yes/No)</th></tr><tr><td>BCBS</td><td>No</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>No</td></tr><tr><td>BCNA</td><td>No</td></tr></table></td></tr>
<tr><td>1.0</td><td>Effective Date: 12/03/2020</td><td>Preliminary drug review</td></tr>
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** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*

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Blue Cross Blue Shield/Blue Care Network of Michigan
Medication Authorization Request Form

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

This form is to be used by participating physicians to obtain coverage for **drugs covered under the medical benefit**. For commercial members only, please complete this form and submit via fax to 1-877-325-5979. If you have any questions regarding this process, please contact BCBSM Provider Relations and Servicing or the Medical Drug Helpdesk at 1-800-437-3803 for assistance.

PATIENT INFORMATION	PHYSICIAN INFORMATION
Name	**Name**
ID Number	**Specialty**
D.O.B. ☐Male ☐Female	**Address**
Diagnosis	**City /State/Zip**
Drug Name	**Phone/Fax: P**: ( ) - **F**: ( ) -
Dose and Quantity	**NPI**
Directions	**Contact Person**
Date of Service(s)	**Contact Person Phone / Ext.**

STEP 1: DISEASE STATE INFORMATION

1. Is this request for: ☐ Initiation ☐ Continuation *Date patient started therapy:* _____
2. Administered by patient or a medical professional? ☐ patient (self) ☐ health care professional (physician, nurse, etc.)
3. Site of administration? ☐ Provider office/Home infusion ☐ Other: _____
   ☐ Hospital outpatient facility (go to #4) *Reason for Hospital Outpatient administration:* _____
4. Please specify location of administration if hospital outpatient infusion: - _____
5. Please provide the NPI number for the place of administration: _____
6. **Initiation AND Continuation of therapy:**
   a. What is the patient's diagnosis? _____
   b. What other medication has the patient received for their condition? Please: list_____
      i. Please describe the response to previous therapies: _____
   c. Will the patient be receiving any other treatment for the listed condition while on this medication? Please list: _____
   d. Please list any labs values important for diagnosing or monitoring this patient's condition: _____
7. **Continuation of therapy:**
   a. Has the patient progressed while on this medication? ☐ yes ☐ no
   b. How has the patient's condition changed while on this medication?
      ☐ Improved: Please describe: _____
      ☐ Stable: please describe: _____
      ☐ Worsened; Please describe: _____
      ☐ Other; Please describe: _____

Chart notes are required for the processing of all requests. Please add any other supporting medical information necessary for our review **(required)**

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Coverage will not be provided if the prescribing physician's signature and date are not reflected on this document.

☐ Request for expedited review: I certify that applying the standard review time frame may seriously jeopardize the life or health of the member or the member's ability to regain maximum function

Physician's Name	**Physician Signature**	**Date**
Step 2: Checklist	☐ Form Completely Filled Out ☐ Provide chart notes	☐ Attach test results
Step 3: Submit	**By Fax: BCBSM Specialty Pharmacy Mailbox 1-877-325-5979**	**By Mail: BCBSM Specialty Pharmacy Program P.O. Box 312320, Detroit, MI 48231-2320**

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