Medical benefit drug policies are a source for WyoBlue Advantage 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.

P&T Date: 06/05/2025

Evkeeza™ (evinacumab-dgnb)

HCPCS: J1305

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 the preferred drugs as listed in WyoBlue Advantage'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 and approval duration 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.

Background Information:

- 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.

- 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.

- 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.

- 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.

- 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 2022 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-C lowering recommends considering adding either ezetimibe or a PCSK9 monoclonal antibody as the initial non-statin therapy. Preference of which agent to add may be influenced by the desired amount of LDL-C-lowering. ACC/AHA guidelines suggest that additional ASCVD risk reduction can be derived by adding ezetimibe to statin therapy, which can lower LDL-C by an additional 13-20%, and placebo-controlled randomized clinical trials have demonstrated favorable safety profiles and additional LDL-C reduction ranging from 43-64% with PCSK9 inhibitors in patients on maximally tolerated statin therapy. The available PCSK9 inhibitors include Repatha® (evolocumab), Praluent® (alirocumab), and Leqvio® (inclisiran). Of these, only Repatha and Praluent have approved indications as adjuncts to other LDL-C lowering therapies for the treatment of HoFH.

- If patients with HoFH have had an inadequate response to statins with or without ezetimine and PCSK9 inhibitors, specialized therapies like Evkeeza, lomitapide, or LDL apheresis may be needed to control LDL-C and, per the 2022 ACC guidance, are best administered under care of a lipid specialist.

- 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 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.

- 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 10 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. Praluent, however, is only approved for adult patients with HoFH.

- 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 5 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.

- 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.

- 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.

References:

1. Evkeeza [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals Inc; March 2023.
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10. Rosenson RS and Durrington P. Familial hypercholesterolemia in adults: Overview. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2021.
11. Rosenson RS and Durrington P. Familial hypercholesterolemia in adults: Treatment. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2021.

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Policy History		
#	Date	Change Description
1.0	Initial Effective Date: 01/01/2026	New policy

** 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.*