Medical Drug Clinical Criteria

Subject:	Evkeeza (evinacumab)		
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Overview

This document addresses the use of Evkeeza (evinacumab), an angiopoietin-like 3 (ANGPTL3) inhibitor monoclonal antibody approved by the Food and Drug Administration (FDA) as an adjunct to other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of individuals aged 5 years and older with homozygous familial hypercholesterolemia (HoFH). The safety and effectiveness of Evkeeza have not been established in individuals with other causes of hypercholesterolemia including those with heterozygous familial hypercholesterolemia (HeFH). Evkeeza is administered via intravenous infusion every 4 weeks.

Familial hypercholesterolemia is an inherited condition caused by genetic mutations which cause high levels of LDL-C at an early age. There are two types of familial hypercholesterolemia (FH). Heterozygous FH (HeFH) is the more common type occurring in approximately 1 in 200 to 250 individuals. Individuals with HeFH have one altered copy of a cholesterol-regulating gene. Homozygous FH (HoFH) is the rare, more severe form, occurring in approximately 1 in 300,000 to 400,000 individuals. Individuals with HoFH have two altered copies of cholesterol-regulating genes. HoFH can cause LDL-C levels more than six times as high as normal (for example, 650-1,000 mg/dL).

Definitive diagnosis of familial hypercholesterolemia is established by genetic confirmation of a mutation in one of the genes critical for low density lipoprotein cholesterol (LDL-C) catabolism. If genetic testing is unavailable, diagnosis can be established though clinical criteria based on LDL-C levels, clinical presentation and family history.

In the clinical setting, statins are considered first-line drug therapy, in addition to healthy lifestyle interventions, in individuals requiring treatment for abnormal cholesterol. Other lipid lowering therapies should be considered second-line options for individuals needing additional cholesterol lowering or who can't tolerate moderate to high doses of statins.

In 2018, the American Heart Association (AHA)/American College of Cardiology (ACC) released guidelines on the management of blood cholesterol. In very high-risk ASCVD, the guidance recommends to consider adding non-statins to statin therapy when LDL-C remains greater than or equal to 70 mg/dL. Ezetimibe is the first agent to consider adding on to maximally tolerated statin therapy. PCSK9 inhibitors can be considered for addition if LDL-C remains greater than or equal to 70 mg/dL on statin therapy combined with ezetimibe.

In 2017, the National Lipid Association (NLA) published recommendations from an expert panel on the use of PCSK9 inhibitors in adults. The panel recommended PCSK9 inhibitor therapy may be considered to further reduce LDL-C in individuals with HoFH, either of unknown genotype or those known to be LDLR defective, on maximally-tolerated statin therapy with or without ezetimibe with a LDL-C greater than or equal to 70 mg/dL or non-HDL-C greater than or equal to 100 mg/dL. The panel indicated PCSK9 therapy appears to be ineffective in individuals with HoFH who are LDLR negative.

Statins have labeled warnings for liver enzyme abnormalities and skeletal muscle effects including myopathy and rhabdomyolysis. Statin-induced adverse events leading to some degree of intolerance is reported in as many as 5% to 30% of individuals although incidence and prevalence vary. The National Lipid Association (NLA) has provided guidance defining statin intolerance as one or more adverse effects associated with statin therapy, which resolves or improves with dose reduction or discontinuation, and can be classified as complete inability to tolerate any dose of a statin or partial intolerance, with inability to tolerate the dose necessary to achieve the individual-specific therapeutic objective. To classify an individual as having statin intolerance, a minimum of two statins should have been attempted, including at least one at the lowest approved daily dosage.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Evkeeza (evinacumab)

Initial requests for Evkeeza (evinacumab) may be approved when the following criteria are met:

I. Individual is 5 years of age or older; **AND**
II. Documentation is provided that individual has Homozygous Familial Hypercholesterolemia (HoFH) verified by (Cuchel 2023):
  A. Presence of two mutant alleles at the LDLR, apoB, PCSK9 or ARH adaptor protein (LDLRAP1) gene locus; **OR**

  B. An untreated LDL-C concentration greater than 400 mg/dL (10 mmol/L) **AND one** of the following:
    1. Cutaneous or tendonous xanthoma before age of 10 years; **OR**
    2. Untreated LDL-C levels consistent with heterozygous familial hypercholesterolemia in both parents (greater than 190 mg/dL);

AND

III. Individual meets one of the following:
  A. Individual is on high intensity statin therapy or statin therapy at the maximum tolerated dose (high intensity statin is defined as atorvastatin 40 mg or higher **or** rosuvastatin 20 mg or higher) (AHA/ACC 2018); **OR**
  B. Individual is statin intolerant based on one of the following:
    1. Inability to tolerate at least two statins, with at least one started at the lowest starting daily dose, demonstrated by adverse effects associated with statin therapy that resolve or improve with dose reduction or discontinuation (NLA 2022); **OR**
    2. Statin associated rhabdomyolysis or immune-mediated necrotizing myopathy (IMNM) after a trial of one statin; **OR**
  C. Individual has a contraindication for statin therapy including but not limited to active liver disease, unexplained persistent elevation of hepatic transaminases or pregnancy;

AND

IV. Individual has had a trial and inadequate response or intolerance to ezetimibe (AHA/ACC 2018);

AND

V. Documentation is provided that individual has had a trial and inadequate response or intolerance to proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor therapy (AHA/ACC 2018); **OR**
VI. Documentation is provided that genetic testing has verified the individual is LDLR negative (NLA 2017).

OR

VII. Individuals 5 - 9 years of age who do not meet RN III, IV, V, or RN III, IV, VI above, may be approved if the following criteria are met:
VIII. Documentation is provided that individual has Homozygous Familial Hypercholesterolemia (HoFH) verified by (Cuchel 2014; Singh 2015):
  A. Presence of two mutant alleles at the LDLR, apoB, PCSK9 or ARH adaptor protein (LDLRAP1) gene locus; OR
  B. An untreated LDL-C concentration greater than 400 mg/dL (10 mmol/L) **AND one** of the following:
    1. Cutaneous or tendonous xanthoma before age of 10 years; **OR**
    2. Untreated LDL-C levels consistent with heterozygous familial hypercholesterolemia in both parents (greater than 190 mg/dL);

AND

IX. Documentation is provided that individual has had a trial and inadequate LDL reduction with at least one other lipid lowering therapy (including but not limited to statin therapy, ezetimibe).

Continuation requests for Evkeeza (evinacumab) may be approved when the following criteria are met:

I. Individual continues to use in combination with lipid lowering therapy (including but not limited to maximally tolerated statin therapy, ezetimibe, PCSK9 inhibitor therapy and/or LDL-C apheresis); **AND**
II. Documentation is provided that individual has achieved LDL-C reduction.

Evkeeza (evinacumab) may not be approved when the above criteria are not met and for all other indications.

Initial Approval Duration: 6 months
Continuation Approval Duration: 1 year

Quantity Limits

Evkeeza (evinacumab) Quantity Limit

Drug	Limit

Evkeeza (evinacumab) 345 mg/2.3 mL, 1200 mg/8 mL	15 mg/kg every 4 weeks

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J1305	Injection, evinacumab-dgnb, 5 mg [Evkeeza]

ICD-10 Diagnosis

E78.00	Pure hypercholesterolemia, unspecified
E78.01	Familial hypercholesterolemia
E78.2	Mixed hyperlipidemia
E78.41	Elevated Lipoprotein(a)
E78.49	Other hyperlipidemia
E78.5	Hyperlipidemia, unspecified

Document History

Revised: 8/16/2024
Document History:

- 8/16/2024 – Annual Review: Update homozygous familial hypercholesterolemia diagnosis criteria; update continuation criteria. Coding Reviewed: Add ICD-10-CM E78.00, E78.2, E78.41, E78.49, and E78.5.
- 8/18/2023 – Annual Review: Update criteria for expanded pediatric indication. Wording and formatting changes. Coding Reviewed: No changes.
- 8/19/2022 – Annual Review: Update statin intolerance criteria. Wording and formatting changes. Coding reviewed: No changes.
- 8/20/2021 – Annual Review: Update statin intolerance criteria. Update guideline references. Coding reviewed: added coding descriptions changes. Effective 10/1/2021 Added HCPCS J1305. Removed J3490, C9399.
- 3/15/2021 – Select Review: Add new criteria and quantity limit for Evkeeza. Coding Reviewed: Added HCPCS J3490, C9399. All diagnosis pend. Effective 7/1/2021, Removed HCPCS C9399, Added HCPCS codes C9079. Added ICD-10-CM E78.01.

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