Evkeeza (evinacumab-dgnb)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Evkeeza policy is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. The indications below including FDA-approved indications and compendial uses are considered covered benefits provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Evkeeza (evinacumab-dgnb) is an ANGPTL3 (angiopoietin-like 3) inhibitor indicated as an adjunct to diet and exercise and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies to reduce LDL-C in adults and pediatric patients, aged 1 year and older, with homozygous familial hypercholesterolemia (HoFH).

POLICY

Required Documentation

The following information is necessary to initiate the prior authorization review:

- Untreated baseline LDL level, LDL levels while receiving statin therapy (prior to initiating therapy with Evkeeza) and current LDL levels on Evkeeza (if applicable)
- Medical records confirming the member is currently on maximally tolerated lipid lowering therapy for both initial requests and continuation requests
- Chart notes demonstrating statin intolerance or contraindication to statin therapy (if applicable)
- Lab results (i.e., LDL-receptor [LDLR], apolipoprotein B [ABOB], proprotein convertase substilisin/Kexin type 9 [PCSK9], or LDL-receptor adaptor protein 1 [LDLRAP1]) or rating scale (i.e. Simon-Broome Diagnostic Criteria or Dutch Lipid Network Criteria) demonstrating HoFH diagnosis

Criteria for Initial Approval

A. Evkeeza (evinacumab-dgnb) may be considered **medically necessary** for the treatment of homozygous familial hypercholesterolemia (HoFH) when **ALL** the following criteria are met:
   1.) Prescriber must be a lipid specialist or a cardiometabolic specialist, unless the member resides in an area where access to these specialists is limited, in which case, the prescriber must be a board-certified cardiologist or endocrinologist.
   2.) Member has a diagnosis of homozygous familial hypercholesterolemia confirmed by ONE of the following:
      a. Genetic diagnosis with documented mutations in both alleles at LDL receptor (LDLR), ApoB, PCSK9, or LDL receptor adaptor protein 1 (LDLRAP1) gene locus or ≥2 such mutations at different loci (Appendix B)
         OR
      b. Clinical diagnosis defined as untreated LDL-C greater than 400 mg/dL plus one of the following:
         i.) Tendon or cutaneous xanthomas before age 10
         ii.) Diagnosis of definite FH by genetic analysis, Simon-Broome Diagnostic Criteria, Dutch Lipid Clinic Network Criteria, or US Make Early Diagnosis to Prevent Early Death (MEDPED) Diagnostic Criteria in both parents (Appendix A)
   3.) Member has been unable to achieve LDL-C of ≤ 70 mg/dL (or < 55 mg/dL with history of multiple clinical atherosclerotic cardiovascular disease [ASCVD] events or one major ASCVD event and multiple high-risk conditions [See Appendix C]) despite adherence† to at least three months of maximally tolerated high-intensity statin therapy and a trial of a PCSK9-targeted therapy (if applicable for age)
   4.) Not to be used in combination with Juxtapid
   5.) Member will continue to receive concomitant lipid-lowering therapy
   6.) Dose does not exceed 15 mg/kg every 4 weeks

OR

   1.) Prescriber must be a lipid specialist or a cardiometabolic specialist, unless the patient resides in an area where access to these specialists is limited, in which case, the prescriber must be a board-certified cardiologist or endocrinologist.
   2.) Member has a diagnosis of homozygous familial hypercholesterolemia confirmed by ONE of the following:
      a. Genetic diagnosis with documented mutations in both alleles at LDL receptor (LDLR), ApoB, PCSK9, or LDL receptor adaptor protein 1 (LDLRAP1) gene locus or ≥2 such mutations at different loci (Appendix B)
         OR
      b. Clinical diagnosis defined as untreated LDL-C greater than 400 mg/dL plus one of the following:
         i.) Tendon or cutaneous xanthomas before age 10
         ii.) Diagnosis of definite FH by genetic analysis, Simon-Broome Diagnostic Criteria, Dutch Lipid Clinic Network Criteria, or US Make Early Diagnosis to Prevent Early Death (MEDPED) Diagnostic Criteria in both parents (Appendix A)
   3.) Member has been unable to achieve an LDL-C of ≤ 70 mg/dL (or < 55 mg/dL with history of multiple clinical atherosclerotic cardiovascular disease [ASCVD] events or one major ASCVD event and multiple high-risk conditions [See Appendix C]) despite adherence to at least three months of a PCSK9-targeted therapy (if applicable for age)
   4.) Member has a documented contraindication (e.g., active liver disease, pregnancy, breastfeeding), or medically justifiable reason that precludes statin use (e.g. member has

experienced rhabdomyolysis, CK elevations ≥ 10x ULN, or statin intolerance defined in accordance with the National Lipid Association [See Appendix D]).
5.) Not to be used in combination with Juxtapid
6.) Dose does not exceed 15 mg/kg every 4 weeks

Approval will be for **6 months**

Continuation of Therapy
The continuation of therapy with Evkeeza may be considered **medically necessary** for members who meet all initial authorization criteria AND all the following:

A. Must have a documented positive clinical response to therapy as defined by achieving or maintaining an LDL-C reduction (i.e., LDL-C is now at goal or 30% reduction of LDL-C from baseline)
B. Member continues treatment with Evkeeza in combination with other LDL-C lowering therapies or has an intolerance or contraindication to other lipid-lowering therapies
C. Dose does not exceed 15mg/kg every 4 weeks

Approval will be for **12 months**

Evkeeza is considered **not medically necessary** for patients who do not meet the criteria set forth above.

†Please note: Documentation of LDL-C levels are required (untreated baseline and current [within 90 days of prior authorization request])

Dosage and Administration
Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Quantity Limit

Trade Name	Generic Name	Quantity Limit
Evkeeza™	evinacumab-dgnb	15 mg/kg every 4 weeks

APPENDIX

APPENDIX A: Diagnosis of familial hypercholesterolemia (FH)
A definite diagnosis of FH is made when one of the following diagnostic criteria is met:

1. Genetic diagnosis
   a) An LDL-receptor mutation, familial defective apo B-100, or a PCSK9 gain-of-function mutation
2. Simon-Broome Diagnostic Criteria for definite FH
   a) Total cholesterol > 290 mg/dL or LDL-C > 190 mg/dL in patients over 16 years of age or total cholesterol > 260 mg/dL or LDL-C > 155 mg/dL in patients less than 16 years of age
   AND
   b) Tendon xanthomas in the patient, first (parent, sibling or child) or second degree relative (grandparent, uncle or aunt)
3. Dutch Lipid Clinic Network Criteria for definite FH
   a) Total score > 8 points

APPENDIX B: Sources of genetic complexity of phenotypic homozygous familial hypercholesterolemia (FH)
Genetic heterogeneity:
LDLR gene loss-of-function variants
ApoB gene-receptor-binding-impaired variants
PCSK9 gene gain-of-function variants

LDLRAP1 gene loss-of-function variants

Variable inheritance patterns:

Semi-dominant (i.e., LDLR, ApoB, PCSK9 genes)

True autosomal recessive (i.e., LDLRAP1 gene)

Variant types:

'Null' variant of LDLR (i.e., copy number variants, nonsense variant resulting in premature termination, splicing variant)

'Defective' variant of LDLR (i.e., missense variant altering a single amino acid residue)

APPENDIX C: Criteria for Identifying Patients at Very High Risk* of ASCVD Events

Major ASCVD Events	Acute coronary syndrome within the past 12 months
	History of myocardial infarction
	History of ischemic stroke
	Symptomatic PAD (claudication with ABI <0.85 or previous revascularization of amputation)
High-Risk Conditions	Age ≥ 65 years
	History of prior coronary artery bypass surgery or PCI outside of the major ASCVD event(s)
	Diabetes
	Hypertension
	Current smoker
	Persistently elevated LDL-C (≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
	History of congestive HF

*Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

APPENDIX D: Statin intolerance in accordance with the National Lipid Association definition

Inability to tolerate at least two statins (one at any dose, one at lowest daily dose) due to objectionable symptoms or abnormal biomarkers temporally related to statin use, reversible upon statin discontinuation and reproducible by re-challenge while excluding other known determinants. Other known determinants include low body mass index (BMI), acute infection, untreated or undertreated hypothyroidism, severe renal or hepatic dysfunction, organ transplant, recent severe trauma, HIV infection, Vitamin D deficiency, history of CK elevation, preexisting or unexplained muscle or joint pain, high level of physical activity, illicit drug abuse, excess alcohol use. Each statin trial, both initial and re-challenge shall be at least two weeks duration.

- A trial of one statin at lowest starting daily dose
  - Rosuvastatin 5mg
  - Atorvastatin 10mg
  - Simvastatin 10mg
  - Lovastatin 20mg
  - Pravastatin 40mg
  - Fluvastatin 40mg
  - Pitavastatin 2mg
- One statin at any daily dose

CLINICAL RATIONALE

Background

HoFH is a rare genetic disorder of lipid metabolism characterized by markedly elevated plasma LDL-C level from birth, which increases the risk of premature atherosclerotic cardiovascular disease (ASCVD) (Raal, 2020). Severe vascular disease including coronary artery disease and aortic stenosis are often seen by adolescent years, and without aggressive LDL-C lowering strategies mortality is common before age of 30

years (National Organization for Rare Disorders [NORD], 2020). HoFH affects 1 in 160,000 individuals to 1 in 300,000 individuals worldwide and is more likely to occur in countries where consanguinity is common (NORD, 2020; Raal, 2020). HoFH occurs when an individual inherits a nonfunctional copy of the familial hypercholesterolemia (FH) genes (e.g., *LDL receptor*, *apolipoprotein B [Apo B]*, *proprotein convertase subtilisin/kexin type 9 [PCSK9]*) from each parent, who carries at least one nonfunctional FH gene (NORD, 2020). Genetic mutations in HoFH are most often caused by the presence of loss-of-function variants in the *LDL receptor*, which leads to impaired hepatic clearance of LDL-C from the circulation (Raal, 2020). True genetic homozygotes have identical mutations in both alleles of the affected gene, but most patients are compound heterozygotes with two different *LDL receptor* mutations (Raal, 2015).

Diagnostic workups for FH include family history, clinical presentation, lipid panel, and genetic testing (NORD, 2020). Once a person is diagnosed with FH, cascade screening (i.e., genetic testing of close relatives) is recommended to identify those with FH before symptoms appear. HoFH can be easily identified in infants and young children by the presence of planar xanthomas (i.e., lipid deposits under the skin), corneal arcus (i.e., lipid deposits in the edge of the cornea), and severely elevated LDL-C (e.g., > 400 mg/dL). In children, noninvasive imaging modalities, such as measurement of carotid intermedia thickness, can help inform treatment decisions.

Efficacy

The efficacy of Evkeeza in the treatment of homozygous familial hypercholesterolemia (HoFH) was evaluated in the ELIPSE phase 3, multinational, randomized, double-blind, placebo-controlled clinical trial. The ELIPSE trial enrolled patients who were ≥ 12 years of age, had a clinical or genotyping diagnosis of HoFH, were receiving stable lipid-lowering therapy (included standalone or a combination of statins, PCSK9 inhibitors, ezetimibe, lipid apheresis, or Juxtapid), had a baseline LDL-C ≥ 70 mg/dL (mean 255 mg/dL), and who were willing to consistently maintain a low-fat diet. Patients were excluded if they had a history of certain cardiovascular conditions, blood pressure > 160 mmHg/100 mmHg, had clinically significant endocrine diseases, used drugs that could alter lipid levels unless controlled and stable, or were pregnant or breastfeeding.

In the ELIPSE trial, patients were randomized to receive Evkeeza (N = 43) 15 mg/kg intravenously every 4 weeks or placebo (n = 22) and were followed for 24 weeks total. The primary endpoint measured was percentage change in LDL-C at 24 weeks and secondary endpoints included absolute change in LDL-C at 24 weeks, percentage change in Apo B, non-HDL-C, TC, and triglyceride levels at 24 weeks, and proportions of patients at 24 weeks with ≥ 30% reduction in LDL-C, ≥ 50% reduction in LDL-C, and LDL-C < 100 mg/dL. Results from the ELIPSE trial are outlined in Table 1. Overall, Evkeeza as an add-on therapy to stable lipid-lowering therapies was well tolerated and significantly reduced LDL-C compared with placebo at 24 weeks in patients with HoFH regardless of the degree of LDL-receptor function.

Table 1. Efficacy of Evkeeza (evinacumab-dgnb) in the Treatment of HoFH

Change from baseline to 24 weeks		**Evkeeza** (n = 43)	**Placebo** (n = 22)	**Least square mean difference (95% CI; p-value if provided)**
LDL-C	**% change**	-47.1%	+1.9%	-49.0 (-65.0 to -33.1; p < 0.001)
	Absolute change	-134.7 mg/dL	-2.6 mg/dL	-132.1 (-175.3 to -88.9; p < 0.001)
Apo B		-41.4%	-4.5%	-36.9 (-48.6 to -25.2; p < 0.001)
Non-HDL-C		-49.7%	+2.0%	-51.7 (-64.8 to -38.5; p < 0.001)
TC		-47.4%	+1.0%	-48.4 (-58.7 to -38.1; p < 0.001)
Triglyceride		-55.0%	-4.6%	-50.4 (-65.6 to -35.2)
• At 24 weeks, a higher % of patients achieved better clinical outcomes with Evkeeza vs. placebo: o ≥ 30% reduction in LDL-C (84% vs. 18%; OR 25.2; p < 0.001) o ≥ 50% reduction in LDL-C (56% vs. 5%; OR 24.2; p = 0.003)				

- LDL-C < 100 mg/dL (47% vs. 23%; OR 5.7, p = not provided)

Safety

Serious hypersensitivity reactions have occurred with Evkeeza (evinacumab-dgnb) (Evkeeza prescribing information, 2021). In clinical trials, one patient (1%) treated with Evkeeza (evinacumab-dgnb) experienced anaphylaxis vs. none in the placebo arm. Evkeeza (evinacumab-dgnb) infusion should be discontinued if signs or symptoms of serious hypersensitivity reactions occur, and patient should be treated for and monitored until hypersensitivity reactions resolve. Therefore, Evkeeza (evinacumab-dgnb) is contraindicated in patients with a history of serious hypersensitivity reaction to evinacumab-dgnb.

Evinacumab-dgnb is a human IgG4 monoclonal antibody, and human IgG is known to cross the placental barrier; therefore, evinacumab-dgnb has the potential to be transmitted from the mother to the developing fetus (Evkeeza prescribing information, 2021). Evkeeza (evinacumab-dgnb) may cause fetal harm when administered to pregnant patients based on animal studies, in which administration of evinacumab-dgnb during organogenesis resulted in increased fetal malformations in rabbits at doses below the human exposure. Patients who may become pregnant should be advised of the risk to the fetus, to obtain a pregnancy test prior to treatment initiation, and to use effective contraception during treatment and for at least 5 months following the last dose of Evkeeza (evinacumab-dgnb).

The most common adverse events reported in subjects treated with Evkeeza during clinical trials (incidence ≥ 3% and more common than placebo) were nasopharyngitis, influenza-like illness, dizziness, rhinorrhea, nausea, pain in extremity, and asthenia. No adverse event reported during clinical trials was associated with drug discontinuation and no deaths occurred in either study arm.

There is potential for immunogenicity with all therapeutic proteins (Evkeeza prescribing information, 2021). In Evkeeza (evinacumab-dgnb) clinical studies, no patients developed treatment-emergent antibodies to evinacumab-dgnb.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD-CM diagnostic codes.

- J1305 – Injection, evinacumab-dgnb (Evkeeza), 5 mg

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POLICY HISTORY

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