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Policy Number: 055.000

Title: Coverage Determination Policy for Evinacumab-dgnb (Evkeeza)

Regions: ☒ **Texas** ☐ **Florida** ☐ **Indiana** ☐ **New Jersey** ☒ **New Mexico**

Impacted Areas:

- ☒ Network Management/Provider Services
- ☐ Member services
- ☐ Quality Management
- ☐ Credentialing
- ☐ IT
- ☐ Administration
- ☐ Compliance/delegation
- ☒ Utilization Management
- ☐ Case management
- ☐ Disease management
- ☒ Claims
- ☐ Human resources
- ☐ Finance
- ☒ Pharmacy
- ☐ ALL

Available LCD/NCD/LCA: None

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Coverage Policy Number: 055.000

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

Initial/New Requests

Evinacumab-dgnb (Evkeeza) is proven and medically necessary for the treatment of **homozygous familial hypercholesterolemia (HoFH)** when **ALL** of the following criteria are met:

1. Diagnosis of homozygous familial hypercholesterolemia (HoFH) as confirmed by **ONE** of the following:
   A. Submission of medical records (e.g., chart notes, laboratory values) confirming genetic confirmation of two mutant alleles at the low density lipoprotein receptor gene (LDLR), Apolipoprotein B-gene (ApoB), the proprotein convertase subtilisin/kexin type 9 gene (PCSK9) or low density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene locus; or
   B. Submission of medical records (e.g., chart notes, laboratory values) confirming **BOTH** of the following:
      I. **ONE** of the following:
         a. Pre-treatment LDL-C greater than 500 mg/dL; or
         b. Treated LDL-C greater than 300 mg/dL or history of treatment with Juxtapid (lomitapide)

AND

      II. **ONE** of the following:
         a. Xanthoma before 10 years of age; or
         b. Heterozygous familial hypercholesterolemia (HeFH) in both parents

2. Patient has failed to achieve an LDL-C goal of < 100 mg/dL despite use of **BOTH** of the following:

A. **ONE** of the following:
   I. Patient is currently treated with maximally tolerated statin therapy plus ezetimibe; or
   II. Patient is unable to tolerate statin therapy as evidenced by **ONE** of the following intolerable and persistent (i.e., more than 2 weeks) symptoms:
      a. Myalgia (muscle symptoms without CK elevations); or
      b. Myositis (muscle symptoms with CK elevations < 10 times upper limit of normal [ULN]); or
      c. Patient has a labeled contraindication to all statins as documented in medical records; or
      d. Patient has experienced rhabdomyolysis or muscle symptoms with statin treatment with CK elevations >10 times ULN

AND

B. **ONE** of the following:
   I. Patient has been treated with PCSK9 therapy or did not respond to PCSK9 therapy; or
   II. Physician attests that the patient is known to have two LDL-receptor negative alleles (little to no residual function) and therefore would not respond to PCSK9 therapy; or
   III. Patient has a history of intolerance or contraindication to PCSK9 therapy; or
   IV. Patient has previously been treated with Juxtapid (lomitapide); or
   V. Patient has previously been treated with lipoprotein apheresis

3. Patient will continue other traditional low-density lipoprotein-cholesterol (LDL-C) lowering therapies (e.g., maximally tolerated statins, ezetimibe) in combination with Evkeeza

4. Evkeeza will not be used in combination with Juxtapid (lomitapide

5. Evkeeza dosing is in accordance with the United States Food and Drug Administration approved labeling

6. Initial authorization will be for no more than 6 months

Renewal/Continuation of Therapy Requests

Continuation of therapy requests for **Evkeeza** for **homozygous familial hypercholesterolemia (HoFH)** will be approved if **ALL** of the following criteria are met:

A. Documentation of a positive clinical response to therapy from pre-treatment baseline
B. Patient continues treatment with other traditional low-density lipoprotein-cholesterol (LDL-C) lowering therapies (e.g., statin, ezetimibe) in combination with Evkeeza
C. Evkeeza will not be used in combination with Juxtapid (lomitapide)
D. Evkeeza dosing is in accordance with the United States Food and Drug Administration approved labeling
E. Reauthorization will be for no more than 12 months

FDA Approved Dose and Indication

FDA Approved Indications	Approved Dosing
Homozygous familial hypercholesterolemia (HoFH) - as an adjunct to other LDL-C lowering therapies for the treatment of adult and pediatric patients, aged 5 years and older	• 15 mg/kg IV over 60 minutes every 4 weeks

NOTE:

- The safety and effectiveness of EVKEEZA have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH)
- The effects of EVKEEZA on cardiovascular morbidity and mortality have not been determined.

General Background

Familial hypercholesterolemia (FH) is an autosomal hereditary disease with 3 major clinical features of - 1) hyper-LDL cholesterolemia, 2) premature Coronary artery disease (CAD) and 3) tendon and skin xanthomas. FH is caused by pathogenic mutations in genes of the low-density lipoprotein (LDL) receptor, apolipoprotein B-100 (Apo-B100) and proprotein convertase subtilisin/kexin type 9 (PCSK9) which play an important role in LDL receptor pathway.
In homozygous familial hypercholesterolemia (HoFH), 2 pathogenic mutations are found in 2 alleles of the causative gene. Consequently, HoFH is characterized by markedly elevated levels of low-density lipoprotein cholesterol (LDL-C) and premature cardiovascular risk. The loss-of function variants in the LDL receptor causes low or zero clearance of LDL-C from circulation. HoFH affects approximately 1 in 300,000 people. If left untreated, mortality is common before age 30.

Evinacumab-dgnb is indicated as an adjunct to other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and pediatric patients, aged 5 years and older, with homozygous familial hypercholesterolemia (HoFH)

Mechanism of Action:

Evinacumab-dgnb is a recombinant human IgG4 isotype monoclonal antibody that binds and inhibits angiopoietin-like protein 3 (ANGPTL3). ANGPTL3 is a regulator of lipoprotein metabolism, affecting lipoprotein lipase- and endothelial lipase-mediated hydrolysis of triglycerides and phospholipids. Inactivity of ANGPLT3 has been associated with potential for correcting hyperlipidemia. Evinacumab-dgnb binds and blocks ANGPTL3 activity, thereby lowering TG and HDL-C by rescuing lipoprotein lipase and endothelial lipase activities. Additionally, evinacumab-dgnb promotes very low-density lipoprotein (VLDL) processing and clearance upstream of LDL formation.

Clinical Evidence

Homozygous familial hypercholesterolemia (HoFH)

ELIPSE HoFH (NCT03399786), was a phase 3, randomized, double-blind, placebo-controlled trial, that evaluated the efficacy of evinacumab in HoFH patients. The study randomly assigned 65 patients, 12 years of age and older, with HoFH who were already stable on lipid-lowering therapy (e.g., maximally tolerated statins, ezetimibe, PCSK9 inhibitor antibodies, lomitapide, and lipoprotein apheresis), in a 2:1 ratio to receive evinacumab or placebo. Most of the trial patients (94%) were receiving a statin (a high-intensity statin in 77%). Additionally, a PCSK9 inhibitor was being administered in 77% of the patients, ezetimibe in 75%, and lomitapide in 25%; 34% of the patients were undergoing apheresis. A total of 63% of the patients were taking at least three lipid modifying drugs. 43 patients were randomized to receive evinacumab 15 mg/kg every 4 weeks and 22 patients to receive placebo. After the double-blind treatment period, 64 of 65 patients entered a 24-week open-label extension period where all patients received evinacumab 15 mg/kg IV every 4 weeks.
The primary outcome was the percent change from baseline in the LDL cholesterol level at week 24. The mean baseline LDL-C was 255 mg/dL. At week 24, the relative risk reduction from baseline was 47.1% in those treated with evinacumab, compared to an increase of 1.9% in the placebo group for a between group least-squares mean (LSM) difference of -49.0 percentage points (95% CI: -65.0, -33.1; $p < 0.001$). The between-group LSM absolute difference in the LDL-C level was -132.1 mg/dL (95% CI: -175.3, -88.9; $p < 0.001$)

In conclusion, in this phase 3 trial, evinacumab substantially lowered LDL cholesterol levels in patients with homozygous familial hypercholesterolemia, regardless of the degree of their LDL-receptor function.

Pediatric Patients (aged 5 to 11 years) with HoFH

Trial R1500-CL-17100 (NCT04233918; Trial 3) was a multicenter, three-part, single-arm, open-label trial in pediatric patients aged 5 to 11 years with HoFH. Part B of this trial evaluated the efficacy of EVKEEZA 15 mg/kg given intravenously every 4 weeks as an adjunct to other lipid-lowering therapies (e.g., statins, ezetimibe, lomitapide, and lipoprotein apheresis) for 24 weeks in 14 patients with HoFH; the mean LDL-C at baseline was 264 mg/dL. At baseline, 86% of patients were on statins, 93% on ezetimibe, 14% on lomitapide, and 50% were receiving lipoprotein apheresis and mean age at baseline was 9 years (range 5 to 11)
The primary efficacy endpoint was percent change in calculated LDL-C from baseline to Week 24. At Week 24, the mean percent change in calculated LDL-C from baseline was −48% (95% confidence interval: −69% to −28%) and the reduction in LDL-C with EVKEEZA was similar across baseline characteristics, including age, sex, limited LDLR activity, concomitant treatment with lipoprotein apheresis, and concomitant background lipid-lowering medications (statins, ezetimibe, and lomitapide).

Professional Societies

The American College of Cardiology/American Heart Association Task Force published their clinical practice guidelines for the management of blood cholesterol in 2018. In regards to those with severe hypercholesterolemia (LDL-C ≥ 190 mg/dL), the guideline recommends

- In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher (≥ 4.9 mmol/L) maximally tolerated statin therapy is recommended (Level I; B-R)
- In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher (≥ 4.9 mmol/L) who achieve less than a 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL or higher (≥ 2.6 mmol/L) ezetimibe therapy is reasonable (Level IIa; B-R)
- In patients 20 to 75 years of age with a baseline LDL-C level 190 mg/dL or higher (≥ 4.9 mmol/L), who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides 300 mg/dL or lower (≤ 3.4 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered (Level IIb; B-R)
- In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL or higher (≥ 2.6 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered (Level IIb; BR)
- In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL or higher (≥ 5.7 mmol/L) and who achieve an ontreatment LDL-C level of 130 mg/dL or higher (≥ 3.4 mmol/L) while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered (Level IIb; C-LD)

The Hyperlipidaemia Education and Atherosclerosis Research Trust United Kingdom (HEART UK) published a consensus statement on a strategy for managing HoFH in the UK and treating to lower lipid targets suggested by the European Atherosclerosis Society (EAS) in 2017. The recommended target LDL-C is < 2.5 mmol/L in adults (< 1.8 mm/L if CVD) and < 3.5 mmol/L in children. With regards to treatment of HoFH, the consensus statement recommends the following:

- Aged 12 and under: Consider lipid apheresis from the age of 2 and no later than 8, combined with maximum tolerated statin, ezetimibe, and bile acid sequestrants (BAS) (if effective).
- Aged over 12: Consider lipid apheresis and evolocumab, unless known LDLR negative, together. Apheresis frequency may be discontinued, be less frequent or not started
- All patients should be offered maximum doses of atorvastatin or rosuvastatin combined with ezetimibe. Other statins may be tried in the event of intolerance
- All HoFH patients on apheresis and standard drug treatment with LDLC above target, who are receptor defective, should have a trial of treatment with evolocumab
- Homozygotes or compound heterozygotes with gain of function PCSK9 alleles or double heterozygotes with, for example, an LDLR defective allele and a gain of function PCSK9 allele (digenic) are likely to respond well to PCSK9 inhibition
- Patients who respond with 10-15% reduction in LDL-C (or interval mean LDL-C if on lipid apheresis) should continue treatment
- Evolocumab should be injected subcutaneously directly after apheresis

- Lomitapide should be considered for adults with HoFH, who have failed to achieve treatment targets while on apheresis and standard drug treatment and have had a trial of evolocumab.
- The frequency of lipid apheresis may be reduced when combined with lomitapide and/or evolocumab.

The Japan Atherosclerosis Society and Asian Pacific Society of Atherosclerosis and Vascular Diseases published guidelines for diagnosis and treatment of familial hypercholesterolemia in 2017. With regards to treatment of HoFH, the guideline recommends the following:

- Intensive lipid-lowering therapy is necessary for the treatment of FH, first-line drug should be statins (recommendation level A, evidence level 3)
- For homozygous FH, consider LDL apheresis and treatment with PCSK9 inhibitors or (microsomal triglyceride protein inhibitor) MTP inhibitors (recommendation level A)

HCPCS Code

HCPCS Code	Description
J1305	Injection, Evinacumab-dgnb (Evkeeza), 5 mg

Acronyms

HoFH = Homozygous familial hypercholesterolemia

LDLR = Low density lipoprotein receptor gene

Apo-B100 = Apolipoprotein B-100

PCSK9 = Proprotein convertase subtilisin/kexin type 9 gene

LDL-C = Low-density lipoprotein cholesterol

CK = Creatine kinase

HeFH = Heterozygous familial hypercholesterolemia

CAD = Coronary artery disease

VLDL = Very low-density lipoprotein

TG = Triglycerides

LPL = Lipoprotein lipase

EL = Endothelial lipase

ANGPTL3 = Angiopoietin-like protein 3

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