09-J3000-99

Original Effective Date: 06/15/21

Reviewed: 04/08/26

Revised: 07/01/26

Subject: Evinacumab-dgnb (Evkeeza®) IV Infusion

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration | Position Statement | Billing/Coding | Reimbursement | Program Exceptions | Definitions

Related Guidelines | Other | References | Updates

DESCRIPTION:

Evinacumab-dgnb (Evkeeza) is an angiopoietin-like protein 3 (ANGPTL3) inhibitor monoclonal antibody first approved by the U.S. Food and Drug Administration (FDA) in February 2021 as an adjunct to other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and pediatric patients, aged 12 years and older, with homozygous familial hypercholesterolemia (HoFH). In March 2023, the indication was expanded to include pediatric patients aged 5 years and older. Use in this age group was supported by the evidence in adults and additional efficacy and safety data from a single-arm, open-label trial in pediatric patients aged 5 to 11 years (i.e., Trial R1500-CL-1710). In September 2025, the indication was expanded to included pediatric patients 1 year and older. Use in this age group was supported by clinical data collected through an expanded access program that required each patient's treating physician to provide adequate documentation to demonstrate that the patient met the eligibility criteria for the program and to provide effectiveness information, including LDL-C values. Four females and two males were enrolled in the program and LDL-C was reduce by 60% at week 40. The updated indication was also reworded as “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)”. Evinacumab was previously granted orphan drug designation for the treatment of HoFH in 2016. ANGPTL3 is expressed primarily in the liver and plays a role in the regulation of lipid metabolism. Inhibition of ANGPTL3 leads to reduction in LDL-C, HDL-C, and triglycerides (TG). Evinacumab reduces LDL-C independent of the presence of LDL receptor (LDLR) by promoting very low-density lipoprotein (VLDL) processing and clearance upstream of LDL formation.

Familial hypercholesterolemia (FH) is an inherited genetic defect that results in severe elevations of blood cholesterol levels and increases the risk of CHD about 20-fold in untreated patients. Recent population data show that the heterozygous and homozygous forms of FH affect one in 200 to 500 and one in 160,000 to 300,000 people, respectively, worldwide. Untreated total cholesterol concentrations in heterozygous FH (HeFH) patients (genetic defect inherited from one parent) are typically in the range of 200 to 450 mg/dL and in homozygotes (genetic defects inherited from both parents) range from 650 to 1,000 mg/dL. Aggressive lipid lowering is necessary to achieve target LDL-C levels (ideally <100 mg/dL or at least a 50% reduction from baseline). Current drug treatments include high-dose statin therapy alone or in combination with other cholesterol lowering medications such as ezetimibe and PCSK9 inhibitors. Statins, on average, decrease LDL-C 15% (range 0 to 48%) in individuals with HoFH. In a phase III trial of patients with HoFH, the PCSK9 inhibitor evolocumab (Repatha), when added to intensive

statin therapy, reduced LDL-C on average by an additional 30% vs. placebo. The oral drug lomitapide (Juxtapid) is specifically FDA-approved for the treatment of HoFH. When added to existing lipid-lowering therapy, lomitapide reduced LDL-C by an average of 40%. Lomitapide has a boxed warning regarding the risk of hepatoxicity and is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). When desired reductions in LDL-C are not achieved with pharmacological therapy, LDL-C apheresis may be used. LDL apheresis can reduce LDL-C by more than 50%; however, the procedure is expensive, not readily available, and inconvenient as it must be done every two weeks.

The safety and efficacy of evinacumab leading to initial FDA approval was evaluated in a multicenter, double-blind, randomized, placebo-controlled trial called ELIPSE-HoFH (NCT03399786) in which evinacumab was compared to placebo in 65 patients with HoFH. During the 24-week, double-blind treatment period, 43 patients were randomized to receive evinacumab 15 mg/kg IV 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 in which all patients received evinacumab. Patients were on a background of other lipid-lowering therapies, including maximally tolerated statins, ezetimibe, PCSK9 inhibitor antibodies, lomitapide, and lipoprotein apheresis. Enrolment was stratified by apheresis status and geographical region. The diagnosis of HoFH was determined by genetic testing or by the presence of the following clinical criteria: history of an untreated total cholesterol (TC) >500 mg/dL and either xanthoma before 10 years of age or evidence of TC >250 mg/dL in both parents. In this trial, 40% (26 of 65) patients had limited LDL receptor (LDLR) function, defined by either <15% receptor function by in vitro assays or by genetic variants likely to result in minimal to no LDLR function by mutation analysis. The mean LDL-C at baseline was 255 mg/dL. In patients with limited LDLR function, the mean LDL-C at baseline was 307 mg/dL. At baseline, 94% of patients were on statins, 75% on ezetimibe, 77% on a PCSK9 inhibitor antibody, 22% on lomitapide, and 34% were receiving lipoprotein apheresis. The mean age at baseline was 42 years (range 12 to 75) with 12% ≥65 years old; 54% women, 3% Hispanic, 74% White, 15% Asian, 3% Black, and 8% Other or not reported.

The primary efficacy endpoint was percent change in LDL-C from baseline to Week 24. At Week 24, the least squares (LS) mean treatment difference between evinacumab and placebo in mean percent change in LDL-C from baseline was −49% (95% confidence interval: −65% to −33%; p <0.0001). At Week 24, the observed reduction in LDL-C with was similar across predefined subgroups, including age, sex, limited LDLR activity, concomitant treatment with lipoprotein apheresis, and concomitant background lipid-lowering medications (statins, ezetimibe, PCSK9 inhibitor antibodies, and lomitapide). After 24 weeks of open-label evinacumab treatment (Week 24 to Week 48), the observed LDL-C reduction from baseline was similar in patients who crossed over from placebo to evinacumab and was maintained in patients who remained on evinacumab for 48 weeks. The detailed results are included the Table below.

Table: Lipid Parameters in Patients in Study ELIPSE-HoFH

	LDL-C	ApoB	Non-HDL-C	TC	TG	HDL-C
Baseline (mean), mg/dL (n=65)	255	171	278	322	124	44
LS Mean: evinacumab (n= 43)	-47%	-41%	-50%	-47%	-55%	-30%
LS Mean: placebo (N = 22)	+2%	-5%	+2%	+1%	-5%	+1%
LS Mean Difference from Placebo (95% CI)	-49% (-65 to -33)	-37% (-49 to -25)	-52% (-65 to -39)	-48% (-59 to -38)	-50% (-66 to -35)	--

Safety data are based on pooled results from two randomized, double-blind, placebo-controlled trials (including ELIPSE-HoFH) that included 81 patients treated with evinacumab Adverse reactions led to discontinuation of treatment in 2 (2%) patients treated with evinacumab, including 1 case of anaphylaxis, and 1 (2%) patient who received placebo. The most common adverse reactions (reported in greater than 3% of evinacumab-treated patients and more frequently than in placebo) included: nasopharyngitis (16% vs. 13%), influenza like illness (7% vs. 6%), dizziness (6% vs. 0%), rhinorrhea (5% vs. 0%), nausea (5% vs. 2%), pain in extremity (4% vs. 0%), and asthenia (4% vs. 0%).

POSITION STATEMENT:

Drug Waste Reduction: Additional medical necessity criteria for dose optimization may apply depending on the requested dose and member's benefit. Refer to Medical Coverage Guideline 09-J5000-54, Drug Waste Reduction.

Site of Care: If evinacumab-dgnb (Evkeeza) is administered in a hospital-affiliated outpatient setting, additional requirements may apply depending on the member's benefit. Refer to 09-J3000-46, Site of Care Policy for Select Non-Oncology Medications.

Initiation of evinacumab (Evkeeza) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "6"):

1. The member has a confirmed diagnosis of homozygous familial hypercholesterolemia (HoFH) validated by **EITHER** of the following ("a" or "b"):
    a. Member has genetic confirmation of **bi-allelic** pathogenic or likely pathogenic variants on different chromosomes at the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* genes **OR** greater than or equal to **TWO** such variants at different loci - *supportive genetic test results or documentation from the medical record must be submitted*
    b. Member has a history of an untreated or treated LDL-C >400 mg/dL), and **EITHER** of the following ("i" or "ii") - *supportive laboratory results and/or documentation from the medical record must be submitted:*
        i. Member had cutaneous or tendon xanthoma occurring before 10 years of age
        ii. **BOTH** of the member's parents have a diagnosis of heterozygous familial hypercholesterolemia (HeFH) (for example, an untreated LDL-C >190 mg/dL)
2. Member has a baseline (within the past 90 days) LDL-C greater than 70 mg/dL despite combination lipid-lowering therapy, when indicated, for at least 90 days - *laboratory results or documentation from the medical record must be submitted.* The lipid-lowering therapy requirements include **ALL** of the following depending on the member's age ("a", "b", and "c"):
    a. **ANY** of the following regarding HMG-CoA reductase inhibitor (statin) therapy ("i", ii", "iii", or "iv"):
        i. Member is receiving high-intensity statin therapy (i.e., rosuvastatin ≥20 mg daily or atorvastatin ≥40 mg daily for members 18 years and older, or rosuvastatin ≥20 mg daily for members less than 18 years of age), **OR**, if high-intensity statin therapy has been attempted and not tolerated, the member is receiving maximally tolerated statin therapy
        ii. The member has confirmed statin intolerance as defined by meeting **ANY** of the following criteria ("1", "2", or "3"):
            1. The member experienced statin-related rhabdomyolysis
            2. The member experienced skeletal-related muscle symptoms (myopathy or myalgia) and **BOTH** of the following:
                - The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products)
                - When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin)
            3. The member experienced elevations in hepatic transaminase while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products)
        iii. The member has an FDA-labeled contraindication or hypersensitivity to both atorvastatin and rosuvastatin – *the specific contraindication(s) must be provided*

iv. The member is less than 7 years of age

b. **EITHER** of the following regarding ezetimibe therapy ("i", "ii", or "iii"):

i. Member is receiving an FDA-recommended dosage of ezetimibe (as single-entity or as combination products)

ii. The member has an FDA-labeled contraindication or hypersensitivity to ezetimibe – *the specific contraindication(s) must be provided*

iii. The member is less than 10 years of age

c. **ANY** of the following regarding PCSK9 inhibitor therapy [e.g., evolocumab (Repatha), alirocumab (Praluent)] ("i", "ii", "iii", or "iv"):

i. Member is receiving an FDA-recommended dosage of evolocumab (Repatha) or alirocumab (Praluent)]

ii. Member has contraindications to treatment with **BOTH** evolocumab (Repatha) and alirocumab (Praluent)] - *the specific contraindication(s) must be provided*

iii. Member is known to have **TWO** LDL-receptor negative alleles - *supportive genetic test results or documentation from the medical record must be submitted*

iv. Member is less than 10 years of age

3. Evinacumab treatment will **NOT** be started in combination with lomitapide (Juxtapid)
4. Treatment is prescribed by, or in consultation with, a cardiologist, endocrinologist, or lipidologist/lipid specialist
5. The member is 15 years of age or older **OR** meets the minimum age as listed in the FDA-approved product labeling for evinacumab
6. The dosage of evinacumab does not exceed 15 mg/kg IV every 4 weeks

Approval duration: 6 months

Continuation of evinacumab (Evkeeza) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "7"):

1. An authorization or reauthorization for evinacumab has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of HoFH (if another health plan, documentation of a health plan-paid claim for evinacumab during the 90 days immediately before the request must be submitted), **OR** the member has previously met **ALL** indication-specific initiation criteria
2. The member has had a beneficial response to evinacumab treatment as evidence by **EITHER** of the following ("a" or "b") - *supportive laboratory results or documentation from the medical record must be submitted:*

   a. Reduction in LDL-C of 20% or more as compared to pretreatment level

   b. LDL-C less than 300 mg/dL

3. Treatment with evinacumab will be used in combination with lipid-lowering therapy including maximally tolerated statin therapy, ezetimibe, and PCSK9 inhibitor therapy unless the member has a documented contraindication, intolerance, or other reasons why use is not appropriate (statin therapy is not required for members less than 7 years of age, and ezetimibe and PCSK9 inhibitor therapy is not required for members less than 10 years of age) - *the specific intolerance(s), contraindication(s), and/or reasons must be provided if applicable*
4. Treatment is prescribed by, or in consultation with, a cardiologist, endocrinologist, or lipidologist/lipid specialist

5. Evinacumab will **NOT** be used in combination with lomitapide (Juxtapid), **UNLESS** the member's LDL-C is still greater than 300 mg/dL despite combination treatment with evinacumab, maximally tolerated statin therapy, ezetimibe (unless contraindicated), and PCSK9 inhibitor therapy (unless contraindicated or inappropriate due two LDL-receptor negative alleles) - *documentation of the member's lipid-lowering treatment history must be submitted if evinacumab used in combination with lomitapide*
6. The member is 15 years of age or older **OR** meets the minimum age as listed in the FDA-approved product labeling for evinacumab
7. The dosage of evinacumab does not exceed 15 mg/kg IV every 4 weeks

Approval duration: 12 months

Evinacumab (Evkeeza) therapy does **NOT** meet the definition of medical necessity for members with heterozygous familial hypercholesterolemia (HeFH) or unspecified familial hypercholesterolemia (i.e., when the subtype is not specified).

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- 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).
- The recommended dose 15 mg/kg administered by IV infusion over 60 minutes once monthly (every 4 weeks). The rate of infusion may be slowed, interrupted or discontinued if the patient develops any signs of adverse reactions, including infusion or hypersensitivity reactions.

Dose Adjustments

- Hepatic impairment - No data are available on evinacumab use in patients with hepatic impairment.
- Renal impairment - Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed in mild or moderate renal impairment. No data are available in patients with severe renal impairment.
- Adverse events – No dosage adjustments are recommended for adverse events.

Drug Availability

- Single-dose vials of 345 mg/2.3 mL (150 mg/mL) and 1,200 mg/8 mL (150 mg/mL)
- Store in a refrigerator at 2 °C to 8 °C (36 °F to 46 °F). Store the vial in the original carton to protect from light. Do not freeze. Do not shake.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Patients with a history of serious hypersensitivity reaction to evinacumab-dgnb or to any of the excipients in Evkeeza.

Precautions/Warnings

- **Serious Hypersensitivity Reactions**: Have occurred with evinacumab in clinical trials. In clinical trials, 1 (1%) evinacumab -treated patient experienced anaphylaxis versus 0 (0%) patients who received placebo. If a serious hypersensitivity reaction occurs, discontinue evinacumab, treat according to standard-of-care and monitor until signs and symptoms resolve.
- **Embryo-Fetal Toxicity**: Evinacumab may cause fetal harm based on animal studies. Advise patients who may become pregnant of the risk to a fetus. Consider obtaining a pregnancy test prior to initiating treatment with evinacumab. Advise patients who may become pregnant to use contraception during treatment and for at least 5 months following the last dose.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J1305	Injection, evinacumab-dgnb, 5 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

E78.010	Homozygous familial hypercholesterolemia [HoFH]

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of guideline creation.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None

RELATED GUIDELINES:

Apheresis, Plasmapheresis and Plasma Exchange, 02-33000-17

Lomitapide (Juxtapid) Oral, 09-J1000-92

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/08/26.

GUIDELINE UPDATE INFORMATION:

06/15/21	New Medical Coverage Guideline.
07/01/21	Added HCPCS code C9079.
10/01/21	Revision: Added HCPCS code J1305 and deleted codes C9079 and J3590.
05/15/22	Review and revision to guideline consisting of updating the position statement and references.
05/15/23	Review and revision to guideline consisting of updating the description section, position statement, dosage/administration, and references. Age limit reduced from 12 to 5 years of age.
09/15/24	Review and revision to guideline consisting of updating the position statement and references. Updated the HoFH diagnosis requirements and added age limits for when certain prerequisite lipid lowering therapy is required.
05/15/25	Review and revision to guideline consisting of updating the position statement and references.
10/01/25	Revision: Added ICD-10 code E78.010 and removed code E78.01.
05/15/26	Review and revision to guideline consisting of updating the position statement, dosage/administration, and references. Age for eligibility expanded to 1 year of age or older. Updated diagnostic criteria for HoFH.
06/01/26	Revision: Added Drug Waste Reduction statement to the Position Statement.
07/01/26	Revision: Added Site of Care statement to the Position Statement.