| Policy and Procedure | |
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| **PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCAR043.1225** | **CARDIOVASCULAR AGENTS**<br>**HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HoFH) AGENTS**<br>**Evkeeza®** (evinacumab-dgnb vial) |
| **Effective Date: 2/1/2026** | **Review/Revised Date**: 05/22, 04/23, 05/24, 05/25, 12/25 (snm) |
| **Original Effective Date: 08/22** | **P&T Committee Meeting Date**: 06/21, 06/22, 06/23, 06/24, 06/25, 12/25 |
| **Approved by: Oregon Region Pharmacy and Therapeutics Committee** | |

**SCOPE:**
Providence Health Plan, Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

**APPLIES TO:**
Medicare Part B

## POLICY CRITERIA:

**COVERED USES:**
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

**REQUIRED MEDICAL INFORMATION:**
For initial authorization, all the following must be met:

1. Diagnosis of Homozygous Familial Hypercholesterolemia (HoFH) as evidenced by either genetic or clinical confirmation, as outlined below:
    a. Genetic confirmation: biallelic functional mutations in the low-density lipoprotein receptor (LDLR), apolipoprotein B (apo B), proprotein convertase subtilisin/kexin type 9 (PCSK9) or LDL receptor adapter protein 1 (LDLRAP1) genes
    b. Clinical confirmation defined as untreated total cholesterol greater than 400 mg/dL or treated LDL-C greater than or equal to 300 mg/dL and one of the following:
        i. Presence of xanthomas before the age of 10 years, or
        ii. Evidence of heterozygous familial hypercholesterolemia in both parents (such as documented history of elevated LDL-C greater than or equal to 190 mg/dL prior to lipid-lowering therapy)
2. Current use of all the following therapies:
    a. High-intensity statin therapy (defined as atorvastatin 40mg - 80mg daily or rosuvastatin 20mg - 40mg daily) unless contraindicated or documented statin intolerance
    b. Ezetimibe, unless contraindicated or prior intolerance
    c. PCSK-9 inhibitor (such as evolocumab), unless contraindicated or prior intolerance

3. Continue to receive concomitant lipid-lowering therapy at the maximally tolerated dose, unless contraindicated or documented intolerance
4. Documentation showing that patient has failed to achieve LDL-C goal (levels taken within the last six months) despite at least six months of use of the therapies outlined above, defined as one of the following:
    a. Treated LDL-C level greater than or equal to 70 mg/dL
    b. Treated LDL-C level greater than or equal to 55 mg/dL and meets either of the following criteria:
        i. History of clinical atherosclerotic cardiovascular disease (ASCVD) event
        ii. Major ASCVD risk factor (e.g., 65 years of age or older, familial hypercholesterolemia, diabetes, chronic kidney disease, history of congestive heart failure)

Initial reauthorization requires documentation of a positive clinical response to therapy, defined as a reduction of 30% or more in LDL-C levels from pre-treatment levels

**EXCLUSION CRITERIA:**
1. Concomitant use of evinacumab-dgnb and lometapide (Juxtapid®)
2. Current pregnancy
3. Diagnosis of Heterozygous familial hypercholesterolemia or other hyperlipidemia disorders

**AGE RESTRICTIONS:**
Age must be appropriate based on FDA-approved indication

**PRESCRIBER RESTRICTIONS:**
Must be prescribed by, or in consultation with, a cardiologist, endocrinologist, or board certified lipidologist

**COVERAGE DURATION:**
Initial authorization will be approved for six months. Reauthorization will be approved until no longer eligible with the plan, subject to formulary and/or benefit changes.

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*Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale,*

*formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.*

*Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.*

## INTRODUCTION:

Evinacumab-dgnb is a monoclonal antibody that binds to and inhibits angiopoietin-like protein 3 (ANGPTL3). Inhibition of ANGPTL3 leads to reductions in LDL-C, HDL-C, and triglycerides (TG). Evinacumab-dgnb 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. Evinacumab-dgnb blockade of ANGPTL3 lowers TG and HDL-C by rescuing LPL and EL activities, respectively.

Recommended dose = 15 mg/kg administered by intravenous (IV) infusion every four weeks.

- Administer the diluted solution via IV infusion over 60 minutes through an IV line containing a sterile, in-line or add-on, 0.2 micron to 5 micron filter.
- Do not mix other medications with evinacumab or administer other medications concomitantly via the same infusion line.

## FDA APPROVED INDICATIONS:

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).

## POSITION STATEMENT:

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder affecting approximately 1 in every 300,000 to 400,000 people.[6] This genetic disorder results from a gene mutation that affects the catabolism of low-density lipoproteins (LDL) and therefore elevates the LDL levels in the blood. The most common mutation that causes HoFH is a loss of function mutation in the low-density lipoprotein receptor (LDLR) gene. Other possible mutations are in the apolipoprotein B (apo B) gene (APOB3500), LDL receptor adapter protein 1 (LDLRAP1) and the proprotein convertase subtilisin kexin 9 (PCSK9) gene – this is a gain of function mutation[6,7].

HoFH is characterized by premature cardiovascular disease due to persistently high levels of LDL cholesterol (LDL-C). Therefore, early diagnosis and treatment is crucial to delay cardiovascular disease in these patients[6,8].

Diagnosis of HoFH can be made through genetic testing or clinical criteria such as baseline LDL levels, physical manifestations and family history. The European Atherosclerosis Society (EAS)[6] criteria for HoFH is defined as one of the following: 1) genetic confirmation of two mutant alleles of the LDLR, Apo(b), PCSK9, or LDLR adaptor protein 1 gene locus; or 2) an untreated LDL-C >500 mg/dL or treated LDL-C ≥300 mg/dL together with either cutaneous or tendon xanthoma before 10 years of age or untreated elevated LDL-C levels consistent with HeFH in both parents. They also indicate lower LDL-C levels do not exclude HoFH. A scientific statement from the American Heart Association (AHA) has proposed a slightly different definition provided in table 1 (see Appendix B)[8].

**American Heart Association/American College of Cardiology Guidelines (2018)**
For patients with primary severe hypercholesterolemia (LDL-C ≥190 mg/dL) initiation of a high intensity statin is recommended. If a high intensity statin is not tolerated then the maximally tolerated statin therapy is recommended. If LDL-C remains ≥100 mg/dL or there is <50% reduction in LDL-C on maximally tolerated statin therapy, the addition of ezetimibe is recommended. If LDL-C remains ≥100 mg/dL consider the addition of a PCSK9 inhibitor. Bile acid sequestrates may be considered in patients who are not eligible for PCSK9 inhibitor.

**Clinical evidence for evinacumab**
*Raal FJ et al. (ELIPSE HoFH Trial) (PubMed ID #* 32813947*)*

- Randomized, Double-Blind, Placebo-Controlled
- Study Duration: 24 weeks
    - Patients receiving placebo during the initial 24-week study period were eligible to enroll in 24 week open label study
- Patient population: Patients (N=65)
    - Key inclusion criteria: Patients with homozygous familial hypercholesterolemia, ≥12 years old, patients were required to receive stable lipid-lowering therapy at the maximally tolerated dose, LDL-C ≥70 mg/dL. If undergoing LDL apheresis – must have initiated at least three months prior to screening and on a stable schedule or stable settings for at least eight weeks.
        - HoFH diagnosis was based on either genetic or clinical criteria results
            - Genetic diagnosis: a documented variant in two LDLR alleles or the presence of homozygous or compound heterozygous variants in apolipoprotein B (APOB) or PCSK9. Patients who had compound heterozygosity or homozygosity for variants

in the gene encoding LDL receptor adaptor protein 1 (LDLRAP1) were also eligible.
    - Clinical diagnosis: untreated total cholesterol level of more than 500 mg per deciliter (12.9 mmol per liter), with either the presence of cutaneous or tendinous xanthomas before the age of 10 years or documentation of an untreated total cholesterol level of more than 250 mg per deciliter (6.5 mmol per liter) in both parents.
  - Key exclusion criteria: Use of nutraceuticals or over-the-counter therapies known to affect lipids without stable doses for at least four weeks prior to screening, newly diagnosed diabetes (within three months prior to randomization visit) or poorly controlled diabetes (HbA1c > 9%), significant cardiac history within three months of screening, pregnant or breastfeeding women, sexually active women not willing to practice highly effective birth control during study period and follow-up.
- Intervention: 2:1 randomization to either evinacumab 15 mg/kg IV every four weeks plus other lipid-lowering therapies or to the placebo group of lipid-lowering therapies alone
- Primary endpoint: Percent change from baseline in the LDL-C level at week 24
- Secondary endpoint: Percentage of participants with ≥30% reduction in calculated low-density lipoprotein cholesterol (LDL-C) at week 24
- Results:
  - Baseline Characteristics: 60% of participants were between 18-44 years old, mean age 41.7±15.5, 74% of participants were white
    - Diagnosis: 68% via genotyping, 32% via clinical diagnosis
    - Cholesterol (mg/dL)
      - Calculated LDL: 255.1±165.2
      - Total cholesterol: 322.3±163.1
    - Adjunct therapies in the evinacumab group:
      - By individual therapy: 93.8% on a statin, 75.4% on ezetimibe, 76.9% on PCSK9 inhibitor, 21.5% on lomitapide, 33.8% undergoing apheresis
      - Combination therapies:
        - Ezetimibe + PCSK9 inhibitor + statin: 44.1% of participants
        - Ezetimibe + lomitapide + PCSK9 inhibitor + statin: 10.8% of participants
        - At least three lipid-lowering therapies: 63.1% of participants
  - Efficacy:

        - Primary endpoint: At week 24, patients in the evinacumab group had a 47.1% reduction from baseline in the LDL-C level, as compared with a 1.9% increase in the placebo group, for a between-group least-squares mean difference of -49.0 percentage points (95% confidence interval [CI], -65.0 to -33.1; P<0.001)
        - Secondary endpoint: at week 24, 83.7% of patients in the evinacumab group had a ≥30% reduction in calculated LDL cholesterol, as compared with 18.2% in the placebo group.
    - Safety:
        - Adverse events during the treatment period occurred in 66% of the patients in the evinacumab group and in 81% of those in the placebo group. No patients discontinued treatment due to an adverse event.
        - Serious adverse events during the treatment period occurred in two patients (5%) in the evinacumab group and were reported as urosepsis and a suicide attempt. Both patients recovered.
        - No cardiovascular events were reported in either group during the double-blind treatment period.
        - An influenza-like illness was reported in five of 44 patients (11%) in the evinacumab group and in no patients in the placebo group.
        - An increase in the level of either alanine or aspartate aminotransferase was reported in two of 44 patients (5%) in the evinacumab group and in two of 21 patients (10%) in the placebo group, increases that were less than three times and five times the upper limit of the normal range, respectively.
- GRADE evidence rating: Low
    - Strengths:
        - A majority of patients were stable on baseline lipid lowering therapies, including ~54% of patients on at least triple therapy
        - Study was multi-site and multi-country, used an intention to treat analysis, included patient's undergoing apheresis
        - Baseline characteristics were well matched between groups
    - Limitations:
        - Study has small patient population, was too short in duration to assess clinical outcomes and was placebo-controlled (for initial 24 weeks)
        - Baseline patient population was mostly white and only included two patients under the age of 18 years

**REFERENCE/RESOURCES**:

1. Evkeeza™ (evinacumab-dgnb) injection for intravenous use [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals; March 2023.
2. Evinacumab-dgnb. IBM Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Accessed April 2, 2021
3. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):e1082-e1143.
4. Raal FJ, Rosenson RS, Reeskamp LF, et al. ELIPSE HoFH Investigators. Evinacumab for Homozygous Familial Hypercholesterolemia. *N Engl J Med*. 2020;383(8):711-720.
5. Rosenson RS, Burgess LJ, Ebenbichler CF, Evinacumab in Patients with Refractory Hypercholesterolemia. N Engl J Med. 2020;383(24):2307-2319.
6. Raal FJ, Hovingh GK Catapano AL. Familial hypercholesterolemia treatments: guidelines and new therapies. *Atherosclerosis*. 2018;277:483-492.Cuchel M, Bruckert E, Ginsberg HN, *et al*; European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J*. 2014 Aug 21;35(32):2146-57.
7. Sturm AC, Knowles JW, Gidding SS, *et al*; Convened by the Familial Hypercholesterolemia Foundation. Clinical Genetic Testing for Familial Hypercholesterolemia: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2018 Aug 7;72(6):662-680.
8. Gidding SS, Champagne MA, de Ferranti SD, *et al*.; American Heart Association Atherosclerosis, Hypertension, and Obesity in Young Committee of Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, Council on Lifestyle and Cardiometabolic Health. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. *Circulation* 2015;132:2167-92.
9. Cuchel M, Raal F, Hegele R, et. al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance, European Heart Journal, Volume 44, Issue 25, 1 July 2023, Pages 2277–2291, https://doi.org/10.1093/eurheartj/ehad197

## Appendix A: BILLING GUIDELINES AND CODING

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| HCPCS | Coding Description | Brand Name |
|---|---|---|
| J1305 | Injection, evinacumab-dgnb, 5 mg | Evkeeza® Vial |
| **ADMINISTRATION CODES◊** | | |
| 96365 | Ther/proph/diag iv inf init | |
| 96366 | Ther/proph/diag iv inf addon | |
| 96413 | Chemo iv infusion 1 hr | |
| 96415 | Chemo iv infusion addl hr | |

◊ Coding/Administration Notes:
• The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
• HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations

## Appendix B:

American Heart Association (AHA)

### Table 1: Homozygous Familial hypercholesterolemia Diagnostic Category from AHA 2015 Scientific Statement

| Clinical Criteria | With Genetic Testing Performed |
|---|---|
| LDL-C ≥400 mg/dL and one or both parents having clinically diagnosed FH, positive genetic testing for a known LDL-C–raising (LDLR, Apo[b], PCSK9) gene defect, or autosomal-recessive FH | Presence of two identical (HoFH) or nonidentical (compound HeFH) abnormal LDL-C–raising gene defects, including the rare autosomal-recessive type |
| If LDL-C >560 mg/dL or LDL-C >400 mg/dL with aortic valve disease or xanthomata at <20 years of age | Occasionally, HoFH will have LDL-C <400 mg/dL |

2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolemia: new treatments and clinical guidance[9]

**Table 2: Updated criteria for the diagnosis of homozygous familial hypercholesterolemia**

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| Clinical criteria<br><br>· LDL-C criteria: Untreated LDL-C >10 mmol/L (>~400 mg/dL) is suggestive of HoFH requiring further investigation to confirm the diagnosis.<br><br>· Additional criteria: Cutaneous or tendon xanthomas before age of 10 years and/or untreated elevated LDL-C levels consistent with heterozygous FH in both parents* *In digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH.<br><br>Genetic criteria<br><br>· Genetic confirmation of bi-allelic pathogenic/likely pathogenic variants on different chromosomes at the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* genes or ≥2 such variants at different loci (*Box 3*); for abbreviations for genetic nomenclature see below. *ABCG5*, *ABCG8*: Genes encoding ATP-binding cassette subfamily G members 5 and 8<br><br>*APOB*: Gene encoding apolipoprotein B *LDLR*: Gene encoding the low-density lipoprotein receptor *LDLRAP1*: Gene encoding low-density lipoprotein receptor adaptor protein 1 *LIPA*: Gene encoding lysosomal acid lipase *PCSK9*: Gene encoding proprotein convertase subtilisin/kexin type 9 protein (PCSK9) |