Clinical Policy: Evinacumab-dgnb (Evkeeza)

Reference Number: HIM.PA.166
Effective Date: 03.01.23
Last Review Date: 02.25
Line of Business: HIM*

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Evinacumab-dgnb (Evkeeza®) is a human monoclonal antibody that binds to angiopoietin-like 3 to block its inhibition of lipoprotein lipase.

**These criteria do NOT apply to California Commercial Exchange Plans; see CP.PHAR.511 for CA Commercial Exchange.*

FDA Approved Indication(s)

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

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Evkeeza is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Homozygous Familial Hypercholesterolemia (must meet all)**:**

1. Diagnosis of HoFH defined as one of the following (a, b, or c):
   a. Genetic mutation indicating HoFH (e.g., mutations in low density lipoprotein receptor [LDLR] gene, proprotein convertase subtilisin kexin 9 [PCSK9] gene, apolipoprotein B [apo B] gene, low density lipoprotein receptor adaptor protein 1 [LDLRAP1] gene);
   b. Treated LDL-C ≥ 300 mg/dL or non-high-density lipoprotein cholesterol (HDL-C) ≥ 330 mg/dL;
   c. Untreated LDL-C ≥ 400 mg/dL, and one of the following (i or ii):
      i. Tendinous or cutaneous xanthoma prior to age 10 years;
      ii. Evidence of familial hypercholesterolemia (heterozygous familial hypercholesterolemia [HeFH] or HoFH) in at least one parent (e.g., documented history of elevated LDL-C ≥ 190 mg/dL prior to lipid-lowering therapy);
2. Prescribed by or in consultation with a cardiologist, endocrinologist, or lipid specialist;
3. Member meets one of the following (a or b):
   a. Both of the following (i and ii):

i. Age ≥ 1 year and < 18 years;
ii. LDL-C ≥ 130 mg/dL within the last 60 days despite statin and ezetimibe therapy, unless member has a contraindication (*see Appendix F*) or history of intolerance to each such therapy;

b. Age ≥ 18 years, and recent (within the last 60 days) LDL-C of one of the following (i or ii):
i. ≥ 70 mg/dL;
ii. ≥ 55 mg/dL if member has ASCVD and is at very high risk (*see Appendix H*);

4. For members ≥ 18 years old and on statin therapy, both of the following (a and b):
a. Evkeeza is prescribed in conjunction with a statin at the maximally tolerated dose;
b. Member has been adherent for at least the last 4 months to maximally tolerated doses of one of the following statin regimens (i, ii, or iii):
i. A high intensity statin (*see Appendix D*);
ii. A moderate intensity statin (*see Appendix D*) and member has one of the following (1 or 2):
1) Intolerance to two high intensity statins;
2) A statin risk factor (*see Appendix F*);
iii. A low intensity statin and member has one of the following (1 or 2):
1) Intolerance to one high and one moderate intensity statins;
2) A statin risk factor (*see Appendix F*) and history of intolerance to two moderate intensity statins;

5. For members ≥ 18 years old and not on statin therapy, member meets one of the following (a or b):
a. Statin therapy is contraindicated per Appendix E;
b. For members who are statin intolerant, both of the following (i and ii):
i. Member has tried at least two statins, one of which must be a hydrophilic statin (pravastatin, fluvastatin, or rosuvastatin);
ii. Member meets one of the following (1 or 2):
1) Member has documented statin risk factors (*see Appendix F*);
2) Member is statin intolerant due to statin-associated muscle symptoms (SAMS) and meets both of the following (a and b):
a) Documentation of intolerable SAMS persisting at least two weeks, which disappeared with discontinuing the statin therapy and recurred with a statin re-challenge;
b) Documentation of re-challenge with titration from lowest possible dose and/or intermittent dosing frequency (e.g., 1 to 3 times weekly);

6. If age ≥ 18 years old, member has been adherent to ezetimibe therapy used concomitantly with a statin at the maximally tolerated dose for at least the last 4 months, unless contraindicated per Appendix E or member has a history of ezetimibe intolerance (e.g., associated diarrhea or upper respiratory tract infection);
7. If age ≥ 10 years old, failure of an 8 week trial of **Repatha®**, unless contraindicated, clinically significant adverse effects are experienced, or member has < 2% LDLR activity;
**Prior authorization may be required for Repatha*

8. If request is for coadministration with Juxtapid®, Leqvio®, Praluent®, or Repatha, member has tried the prior therapy for at least 3 consecutive months with inadequate response defined as failure to achieve LDL-C ≤ 250 mg/dL or a 20% reduction in LDL-C from baseline;
9. Documentation of member's current weight in kg;
10. Dose does not exceed 15 mg/kg every 4 weeks.

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: HIM.PA.33 for health insurance marketplace; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: HIM.PA.103 for health insurance marketplace; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: HIM.PA.154 for health insurance marketplace.

II. Continued Therapy

A. Homozygous Familial Hypercholesterolemia (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. If statin tolerant, documentation of adherence to a statin at the maximally tolerated dose;
3. Member is responding positively to therapy as evidenced by lab results within the last 3 months showing an LDL-C reduction since initiation of Evkeeza therapy;
4. Documentation of member's current weight in kg;
5. If request is for a dose increase, new dose does not exceed 15 mg/kg every 4 weeks.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: HIM.PA.33 for health insurance marketplace; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: HIM.PA.103 for health insurance marketplace; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: HIM.PA.154 for health insurance marketplace.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – HIM.PA.154 for health insurance marketplace, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALT: alanine transaminase
apo B: apolipoprotein B
ARH: autosomal recessive hypercholesterolemia
ASCVD: atherosclerotic cardiovascular disease
eGFR: estimated glomerular filtration rate
FDA: Food and Drug Administration
HDL-C: high-density lipoprotein cholesterol
HeFH: heterozygous familial hypercholesterolemia
HoFH: homozygous familial hypercholesterolemia
LDL-C: low density lipoprotein cholesterol
LDLR: low density lipoprotein receptor
LDLRAP1: low density lipoprotein receptor adaptor protein 1
PCSK9: proprotein convertase subtilisin kexin 9
SAMS: statin-associated muscle symptoms
ULN: upper limit of normal

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
ezetimibe/simvastatin (Vytorin®)	10/40 mg PO QD	10 mg-40 mg/day (use of the 10/80 mg dose is restricted to patients who have been taking simvastatin 80 mg for 12 months or more without evidence of muscle toxicity)
ezetimibe (Zetia®)	10 mg PO QD	10 mg/day
atorvastatin (Lipitor®)	40 mg PO QD	80 mg/day
rosuvastatin (Crestor®)	5 - 40 mg PO QD	40 mg/day
pravastatin (Pravachol®)	10 - 80 mg PO QD	80 mg/day
fluvastatin (Lescol®)	20 - 80 mg PO QD	80 mg/day
Repatha® (evolocumab)	420 mg SC once monthly	420 mg/month

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): history of serious hypersensitivity reactions to evinacumab-dgnb or to any of the excipients in Evkeeza
- Boxed warning(s): none reported

Appendix D: High and Moderate Intensity Daily Statin Therapy for Adults

High Intensity Statin Therapy ***Daily dose shown to lower LDL-C, on average, by approximately ≥50%***
• Atorvastatin 40-80 mg • Rosuvastatin 20-40 mg
Moderate Intensity Statin Therapy ***Daily dose shown to lower LDL-C, on average, by approximately 30% to 50%***
• Atorvastatin 10-20 mg • Fluvastatin XL 80 mg • Fluvastatin 40 mg BID • Lovastatin 40 mg • Pitavastatin 1-4 mg • Pravastatin 40-80 mg • Rosuvastatin 5-10 mg • Simvastatin 20-40 mg
Low Intensity Statin Therapy ***Daily dose shown to lower LDL-C, on average, by <30%***
• Simvastatin 10 mg • Pravastatin 10-20 mg • Lovastatin 20 mg • Fluvastatin 20-40 mg

Appendix E: Statin and Ezetimibe Contraindications

Statins
• Decompensated liver disease (development of jaundice, ascites, variceal bleeding, encephalopathy) • Laboratory-confirmed acute liver injury or rhabdomyolysis resulting from statin treatment • Pregnancy*, actively trying to become pregnant, or nursing • Immune-mediated hypersensitivity to the HMG-CoA reductase inhibitor drug class (statins) as evidenced by an allergic reaction occurring with at least TWO different statins
Ezetimibe
• Moderate or severe hepatic impairment [Child-Pugh classes B and C] • Hypersensitivity to ezetimibe (e.g., anaphylaxis, angioedema, rash, urticaria)

**In July 2021, the FDA requested removal of the contraindication against use of statins in pregnant women. Because the benefits of statins may include prevention of serious or potentially fatal events in a small group of very high-risk pregnant patients, contraindicating these drugs in all pregnant women is not appropriate. https://www.fda.gov/safety/medical-product-safety-information/statins-drug-safety-communication-fda-requests-removal-strongest-warning-against-using-cholesterol*

Appendix F: Statin Risk Factors

Statin Risk Factors
• Multiple or serious comorbidities, including impaired renal or hepatic function • Unexplained alanine transaminase (ALT) elevations > 3 times upper limit of normal, or active liver disease • Concomitant use of drugs adversely affecting statin metabolism • Age > 75 years, or history of hemorrhagic stroke • Asian ancestry

Appendix G: General Information

- Low density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene is also known as autosomal recessive hypercholesterolemia (ARH) adaptor protein 1 gene.
- The diagnosis of SAMS is often on the basis of clinical criteria. Typical SAMS include muscle pain and aching (myalgia), cramps, and weakness. Symptoms are usually bilateral and involve large muscle groups, including the thigh, buttock, back, and shoulder girdle musculature. In contrast, cramping is usually unilateral and may involve small muscles of the hands and feet. Symptoms may be more frequent in physically active patients. Symptoms often appear early after starting stain therapy or after an increase in dose and usually resolve or start to dissipate within weeks after cessation of therapy, although it may take several months for symptoms to totally resolve. Persistence of symptoms for more than 2 months after drug cessation should prompt a search for other causes or for underlying muscle disease possibly provoked by statin therapy. The reappearance of symptoms with statin rechallenge and their disappearance with drug cessation offers the best evidence that the symptoms are truly SAMS.
- Pravastatin, fluvastatin, and rosuvastatin are hydrophilic statins which have been reported to confer fewer adverse drug reactions than lipophilic statins.
- According to the Repatha Prescribing Information, patients known to have two LDLR negative alleles (little to no residual function) did not respond to Repatha, with negative defined as < 2% uptake in the TESLA pivotal study. In contrast, patients with < 2% activity did respond to Evkeeza in the ELIPSE HoFH pivotal study.

Appendix H: Criteria for Defining Patients at Very High Risk of Future ASCVD Events[3]
Very high risk is defined as having either a history of multiple major ASCVD events **OR** 1 major ASCVD event and multiple high-risk conditions:

- Major ASCVD events:
  - Recent acute coronary syndrome (within the past 12 months)
  - History of myocardial infarction (other than recent acute coronary syndrome event listed above)
  - History of ischemic stroke

- Symptomatic peripheral artery disease (history of claudication with ankle-brachial index < 0.85 or previous revascularization or amputation)

- High-risk conditions:
  - Age ≥ 65 years
  - HeFH
  - History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
  - Diabetes
  - Hypertension
  - Chronic kidney disease (estimated glomerular filtration rate [eGFR] 15-59 mL/min/1.73 m^2)
  - Current tobacco smoking
  - Persistently elevated LDL-C (LDL-C ≥ 100 mg/dL [≥ 2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
  - History of congestive heart failure

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
HoFH	15 mg/kg IV every 4 weeks	15 mg/kg/4 weeks

VI. Product Availability

Solution for injection in single-dose vials: 345 mg/2.3 mL (150 mg/mL), 1,200 mg/8 mL (150 mg/mL)

VII. References

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2. Raal FJ, Rosenson RS, Reeskamp LF, et al. Evinacumab for homozygous familial hypercholesterolemia. N Engl J Med 2020;383:711-20.

Guidelines

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Statin Tolerance

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11. Manpuya WM, Cho L, Frid D, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. American Heart Journal 2013;166(3):597-603.
12. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings. Ann of Intern Med 2013;158(7):526-34.
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15. Warden BA, Guyton JR, Kovacs AC, et al. Assessment and management of statin-associated muscle symptoms (SAMS): A clinical perspective from the National Lipid Association. J Clin Lipidol. 2023 Jan-Feb;17(1):19-39. doi: 10.1016/j.jacl.2022.09.001.
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Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J1305	Injection, evinacumab-dgnb, 5 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created: adapted from previously approved policy CP.PHAR.511; per 2022 ACC expert consensus decision pathway, lowered minimum LDL requirement to 55 mg/dL for members with ASCVD at very high risk and added corresponding Appendix H;	11.09.22	02.23

Reviews, Revisions, and Approvals	Date	P&T Approval Date
updated HCPCS codes with drug-specific code; references reviewed and updated.		
RT4: updated FDA approved pediatric extension from ≥ 12 years to ≥ 5 years for HoFH.	03.28.23	
1Q 2024 annual review: for redirection to Repatha added requirement for 8 week trial duration; added Leqvio to list of potential co-administered drugs along with Juxtapid, Praluent, and Repatha; divided criteria with multiple elements into separate bullets for added clarity; Appendix H clarified smoking is specific to tobacco; references reviewed and updated.	10.09.23	02.24
1Q 2025 annual review: per 2022 ACC expert consensus decision pathway, lowered untreated LDL requirement to 400 mg/dL and revised evidence of HeFH in both parents to evidence of familial hypercholesterolemia in at least one parent; modified redirection to Repatha to apply only to age ≥ 10 years old per Repatha FDA-approved indication for HoFH; references reviewed and updated.	10.31.24	02.25
RT4: updated FDA approved pediatric extension from ≥ 5 years to ≥ 1 years for HoFH.	09.30.25	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a

discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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