Policy Number	**RX501.136**
Policy Effective Date	**04/01/2025**

Evinacumab-dgnb

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted

study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Evinacumab-dgnb (Evkeeza™) **may be considered medically necessary** when all of the following criteria are met:

- 5 years of age or older; **AND**
- Diagnosis of homozygous familial hypercholesterolemia defined by ONE of the following:
    - Documented variant in two low-density lipoprotein receptor (LDLR) alleles; or
    - Presence of homozygous or compound heterozygous mutations in apolipoprotein B (ApoB) or pro-protein convertase subtilisin/kexin 9 (PCSK9); or
    - Presence of compound heterozygosity or homozygosity for variants in the gene encoding low-density lipoprotein receptor adaptor protein 1 (LDLRAP1); or
    - Untreated low-density lipoprotein-cholesterol (LDL-C) >500mg/dL, with either cutaneous or tendinous xanthoma before the age of 10 years or documentation of an untreated LDL-C ≥190mg/dL in both parents; or
    - Treated LDL-C ≥300mg/dL, with either cutaneous or tendinous xanthoma before the age of 10 years or documentation of an untreated LDL-C ≥190mg/dL in both parents; **AND**
- Low-density lipoprotein-cholesterol (LDL-C) is currently greater than 70mg/dL despite treatment on maximally tolerated combination lipid lowering therapy (e.g., statins, ezetimibe, Repatha).

The use of Evinacumab-dgnb (Evkeeza™) for all other indications, including but not limited to heterozygous familial hypercholesterolemia, **is considered experimental, investigational and/or unproven.**

Policy Guidelines

None.

Description

Homozygous Familial Hypercholesterolemia

Homozygous familial hypercholesterolemia (HoFH) is a rare and life-threatening inherited disorder characterized by markedly elevated low-density lipoprotein (LDL) levels, physical exam signs of cholesterol deposition, and premature cardiovascular disease. The first major cardiovascular events often occur during adolescence, but angina pectoris, myocardial infarction and death have also been reported in early childhood. (1) Although HoFH was

historically thought to affect 1 in a million, new research has shown that HoFH prevalence is likely higher, with as many as 1 in 170,000 to 300,000 individuals affected. (1, 2)

HoFH is most often caused by the presence of loss-of-function variants of the low-density lipoprotein receptor (LDLR). It can also be caused by mutations of the apolipoprotein B (ApoB) binding site on LDLRs, pro-protein convertase subtilisin/kexin 9 (PCSK9), and low-density lipoprotein receptor adaptor protein 1 (LDLRAP1). LDLRs are responsible for about 70% of the uptake of circulating low-density lipoprotein-cholesterol (LDL-C) molecules into the liver. Deficiency or absence of the LDLRs allow for accelerated deposition of cholesterol on the walls of the arteries, causing them to harden and narrow, and ultimately leading to a reduction in the flow of blood with resultant cardiovascular diseases such as stroke and myocardial infarction. (1, 2)

Diagnosis

In the primary care setting, the diagnosis of HoFH may be easily missed therefore, early diagnosis of HoFH and prompt initiation of diet and lipid-lowering therapy are critical. Genetic testing may provide a definitive diagnosis, but if unavailable, markedly elevated LDL-C levels together with cutaneous or tendon xanthomas before 10 years, or untreated elevated LDL-C levels consistent with heterozygous FH in both parents, are suggestive of HoFH. Individuals with suspected HoFH should be promptly assessed by specialized centers for a comprehensive atherosclerotic cardiovascular disease (ACVD) evaluation and clinical management. Unfortunately, patients are commonly only identified after experiencing a cardiovascular event at an unexpected age or as a result of a family member being diagnosed. While genetic testing may provide a definitive diagnosis of HoFH, it is recognized that in some patients, genetic confirmation remains elusive. (1, 2)

Treatment

Reducing the burden of elevated LDL-C is critical given the atherosclerotic cardiovascular complications associated with HoFH. Although a low-saturated fat, low-cholesterol, heart-healthy diet should be recommended for all patients with HoFH, diet has little impact on the severity of hypercholesterolemia, even with strict adherence. (1) First-line treatment is maximally tolerated statin therapy and should be started as early as possible. LDL apheresis can be considered as an alternative when LDL-C does not adequately respond to medical therapy. Apheresis can be cumbersome, as it involves need for venous access and either weekly or biweekly sessions. In recent years, a number of new LDL lowering therapies have emerged. (3) The 2018 American Heart Association (AHA)/American College of Cardiology (ACC) Multisociety Guideline on the Management of Blood Cholesterol indicates that a LDL-C threshold of 70 mg/dL (1.8 mmol/L) should be used to consider addition of nonstatin therapy to maximally tolerated statin therapy. (4)

Evinacumab-dgnb

Evinacumab-dgnb is a recombinant human monoclonal antibody that binds to and inhibits ANGPTL3. ANGPTL3 is a member of the angiopoietin-like protein family that is expressed primarily in the liver and plays a role in the regulation of lipid metabolism by inhibiting

lipoprotein lipase (LPL) and endothelial lipase (EL). Evinacumab-dgnb inhibition of ANGPTL3 leads to reduction in LDL-C, high-density lipoprotein cholesterol (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. (5)

Regulatory Status

Evkeeza™ was 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. The FDA label states the safety and efficacy has not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia. In March 2021, Evkeeza™ was approved for pediatric patients, aged 5-11 with homozygous familial hypercholesterolemia. (5)

Rationale

Clinical Studies

Adults and Pediatric Patients Aged 12 Years and older with HoFN

Study ELIPSE-HoFH (NCT03399786, Trial 1) was a multicenter, double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of Evkeeza compared to placebo in 65 patients with homozygous familial hypercholesterolemia (HoFH) (63 adult patients and 2 pediatric patients). During the 24-week, double-blind treatment period, 43 patients were randomized to receive Evkeeza 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 Evkeeza 15 mg/kg IV every 4 weeks. (5)

Patients were on a background of other lipid-lowering therapies, including maximally tolerated statins, ezetimibe, pro-protein convertase subtilisin/kexin 9 (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.

Baseline Disease and Demographic Characteristics

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 be genetic variants likely to result in minimal to no LDLR function by mutation analysis. (5)

The mean low-density lipoprotein-cholesterol (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. (5)

Endpoint Results

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 Evkeeza and placebo in mean percent change in LDL-C from baseline was -49% (95% confidence interval: -65% to -33%; p <0.0001). After 24 weeks of open-label Evkeeza treatment (Week 24 to Week 48), the observed LDL-C reduction from baseline was similar in patients who crossed over from placebo to Evkeeza and was maintained in patients who remained on Evkeeza for 48 weeks. For efficacy results see Table 1. (5)

Table 1. Lipid Parameters in Patients (63 Adults and 2 Pediatric Patients) with HoFH on Other Lipid-Lowering Therapies in Trial ELIPSE-HoFH (Trial 1) (5)

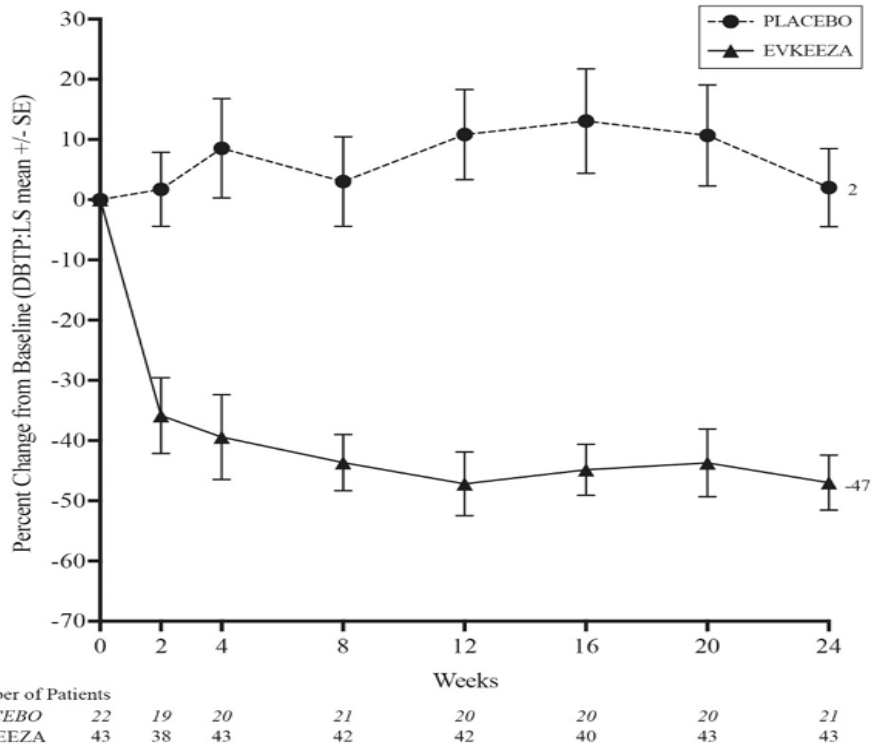
	LDL-C	ApoB	Non-HDL-C	TC	TG[a]	HDL-C[a]
Baseline (mean), mg/dL (N=65)	255	171	278	322	124	44
LS Mean: Evkeeza (N=43)	-47%	-41%	-50%	-47%	-55%	-30%[b]
LS Mean: Placebo (N=22)	+2%	-5%	+2%	+1%	-5%	+1%[b]
LS Mean Difference from Placebo (95% CI)	-49% (-65 to -33)	-37% (-49 to -25)	-52% (-65 to -39)	-48% (-59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

ApoB: apolipoprotein B, CI: confidence interval, HDL-C: high-density lipoprotein-cholesterol, HoFH: homozygous familial hypercholesterolemia, LDL-C: low-density lipoprotein-cholesterol, LS mean: least squares mean, N: number of randomized patients, TC: total cholesterol, TG: triglycerides.

[a] Neither TG nor HDL-C were pre-specified in the hypothesis testing.

[b] Mean percent change, based on safety population (Evkeeza, n=44; placebo, n=20); HDL-C is presented for completeness but was not an efficacy endpoint that was statistically analyzed. One subject in the placebo group discontinued the study before Week 24. The treatment difference and 95% confidence interval (CI) were estimated using a mixed model repeated measures analysis.

Figure 1: Calculated LDL-C LS Mean Percent Change from Baseline Over Time Through Week 24 in Patients (63 Adults and 2 Pediatric Patients) with HoFH in Trial ELIPSE-HoFH (Trial 1)



LS mean: least squares mean, HoFH: homozygous familial hypercholesterolemia, DBTP: double blind treatment period, SE: standard error.

Pediatric Patients (aged 12 to 17 years) with HoFH

In an open-label extension trial (Trial 2) 13 pediatric patients with HoFH received 15 mg/kg IV of Evkeeza every 4 weeks as an adjunct to other lipid-lowering therapies (e.g., statins, ezetimibe, PCSK9 inhibitor antibodies and lipoprotein apheresis) for a median treatment duration of 33 weeks. The mean percent change from baseline in LDL-C at Week 24 was -52% in the 9 patients who completed treatment and had a lipid assessment at Week 24. Overall, the effect of evinacumab-dgnb on lipid parameters in pediatric patients with HoFH was generally similar to that seen in adults with HoFH. (5)

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.

Baseline Disease and Demographic Characteristics

In Part B, 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.

The mean age at baseline was 9 years (range 5 to 11); 57% females; 0% Hispanic; 57% White, 14% Asian, 7% Black or African American, 7% American Indian or Alaska Native, and 14% other races. Mean body weight was 40 kg. Body mass index (BMI) was 20 kg/m_2.

Endpoint Results
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%). For efficacy results see Table 2. HDL-C and TG reductions observed in this trial were similar to changes seen in Trial 1, see Table 1.

At Week 24, 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).

Table 2. Lipid Parameters in evkeeza -Treated Pediatric Patients (aged 5 to 11 years) with HoFH Who Received Concomitant Lipid-Lowering Therapies (Trial 3)

	LDL-C	ApoB	Non-HDL-C	TC
Baseline (mean) (N=14)	264 mg/dL	168 mg/dL	282 mg/dL	316 mg/dL
Percent Change from Baseline at Week 24 (95% CI)	-48 (-69 to -28)	-41 (-59 to -24)	-49 (-68 to -30)	-49 (-65 to -33)

HoFH: homozygous familial hypercholesterolemia, N: number of randomized patients, CI: confidence interval.

UpToDate
In 2023, UpToDate published guidance for the treatment of adults with familial hypercholesterolemia which offered the following recommendations for the treatment of HoFH (6):

- Adult patients with HoFH often have untreated LDL-C values >500 mg/dL, are at very high risk of developing potentially lethal atherosclerotic cardiovascular disease at a very young age.
- In addition to a high-dose statin (atorvastatin 80 mg daily or rosuvastatin 40 mg daily), most homozygous patients will require a combination of additional therapies such as ezetimibe, a PCSK9 inhibitor, and potentially LDL-C apheresis. The care of such patients should involve a lipid specialist if one is available.

In 2023, UpToDate published guidance for the treatment of children with familial hypercholesterolemia (FH) which offered the following recommendations for the clinical

diagnosis of HoFH. (7) Criteria includes: Untreated LDL-C >500 mg/dL (>13 mmol/L) or treated LDL-C ≥300 mg/dL (>8 mmol/L), plus either of the following:

- Cutaneous or tendon xanthoma before age 10 years, or
- Elevated LDL-C levels consistent with heterozygous FH in both parents

It is important to note, however, that untreated LDL-C levels <500 mg/dL may be seen in some individuals with HoFH, particularly in very young children, and genetic testing should be considered to further clarify the diagnosis. A definitive diagnosis of FH can be made by identifying causative mutation(s) in the LDLR, APOB, and PCSK9 genes.

Summary of Evidence

Based on the clinical studies provided to the U.S. Food and Drug Administration (FDA) for approval, evinacumab-dgnb (Evkeeza™) may be considered conditionally medically necessary for the FDA labeled indication 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 when the above criteria are met.

The FDA label for evinacumab-dgnb (Evkeeza™) states the safety and efficacy has not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia.

Professional Guidelines and Position Statements

Several guidelines provide strategies for managing familial hypercholesterolemia, including HoFH.

European Atherosclerosis Society (1)

In 2014, the European Atherosclerosis Society (EAS) Consensus Panel published guidance on the diagnosis and clinical management of HoFH (1 which offered the following criteria for the diagnosis of HoFH:

- "Genetic confirmation of two mutant alleles at the LDLR, APOB, PCSK9, or LDLRAP1 gene locus; OR
- An untreated LDL-C >13 mmol/L (500 mg/dL) or treated LDL-C ≥8 mmol/L (300 mg/dL)* together with either:
    - Cutaneous or tendon xanthoma before age 10 years; or
    - Untreated elevated LDL-C levels consistent with heterozygous FH in both parents

* These LDL-C levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude HoFH."

American College of Cardiology/American Heart Association Task Force (3)

In 2020, the American College of Cardiology/American Heart Association Task Force published Guidance related to the diagnosis and treatment for familial hypercholesterolemia and state: "In patients with severe primary hypercholesterolemia (LDL-C ≥ 190 mg/dL) begin high-intensity statin therapy. If the LDL-C levels remains ≥ 100 mg/dL, add ezetimibe. If the LDL-C remains ≥ 100 mg/dL on this regimen, consider a PCSK9 inhibitor if the patient has multiple risk factors that increase the risk of ASCVD. Other therapies can also be used (e.g., bile acid sequestrants)".

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J1305

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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7. deFerranti S. Familial hypercholesterolemia in children. In: UpToDate, Fulton D (Ed), UpToDate, Waltham, MA. Available at <https://www.uptodate.com> (accessed February 9, 2024).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
04/01/2025	Reviewed. No changes.
04/15/2024	Document updated with literature review. The following change was made to Coverage: Changed age of individuals from "12 years of age or older" to "5 years of age or older". No new references added; some updated.
04/15/2023	Document updated with literature review. The following change was made to Coverage: Modified conditional criteria under "diagnosis of homozygous familial hypercholesterolemia". Added references 2, 6, 7; others updated.
07/01/2022	Reviewed. No changes.
08/15/2021	New medical document. Evinacumab-dgnb (Evkeeza™) may be considered medically necessary for the diagnosis of homozygous familial hypercholesterolemia when specific criteria are met. The use of Evinacumab-dgnb (Evkeeza™) for all other indications, including but not limited to heterozygous familial hypercholesterolemia, is considered experimental, investigational and/or unproven.