Medical Policy Bulletin

Title:
Evinacumab-dgnb (Evkeeza)
Policy #:
MA08.133c

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

MEDICALLY NECESSARY

INITIAL THERAPY

Evinacumab-dgnb (Evkeeza) is considered medically necessary and, therefore, covered for the treatment of individuals 5 years of age or older with homozygous familial hypercholesterolemia (HoFH) when all of the following criteria, including dosing and frequency, are met:

- Documented diagnosis of HoFH confirmed by **one** of the following:
  - Documentation of the presence of pathogenic variations at two alleles at the low-density lipoprotein receptor (LDL-R), apolipoprotein B (APO-B), proprotein convertase subtilisin-kexin type 9 (PCSK9) or low-density lipoprotein receptor adaptor protein-1 (*LDLRAP1*) gene locus.
  - Untreated low-density lipoprotein cholesterol (LDL-C) greater than 500 mg/dL **or** treated LDL-C greater than or equal to 300 mg/dL and **one** of the following:
    - Cutaneous or tendinous xanthomas before 10 years of age
    - Documentation of untreated total cholesterol greater than 250 mg/dL in both parents
- Individual currently has elevated LDL-C levels and meets the criteria for each age group:
  - Individuals 10 years of age and older: LDL-C 100 mg/dL or greater despite receiving all of the following therapies for at least 12 weeks, unless documented failure, contraindication, or intolerance, and will continue these therapies while on evinacumab-dgnb (Evkeeza):
    - Maximally tolerated moderate- or high-intensity statin therapy (e.g., atorvastatin, rosuvastatin, simvastatin)
    - Ezetimibe (Zetia)
    - PCSK9 inhibitor (e.g., alirocumab [Praluent], evolocumab [Repatha]), unless individual has two LDLR-negative alleles
  - Individuals 5 to less than 10 years of age: LDL-C 100 mg/dL or greater (no prior therapies required)

- Dosing and frequency: 15 mg/kg administered by intravenous (IV) infusion once monthly (every 4 weeks)

CONTINUATION THERAPY

Continuation of evinacumab-dgnb (Evkeeza) is considered medically necessary and, therefore, covered when the individual continues to receive other lipid-lowering therapy (unless documented failure, contraindication, or intolerance) and has a documented reduction in LDL-C of at least 30% since initiation of therapy.

EXPERIMENTAL/INVESTIGATIONAL

All other uses for evinacumab-dgnb (Evkeeza), including the treatment of other causes of hypercholesterolemia (e.g., heterozygous familial hypercholesterolemia [HeFH]), are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

DOSING AND FREQUENCY REQUIREMENTS

The Company reserves the right to modify the Dosing and Frequency Requirements listed in this policy to ensure consistency with the most recently published recommendations for the use of evinacumab-dgnb (Evkeeza). Changes to these guidelines are based on a consensus of information obtained from resources such as, but not limited to: the US Food and Drug Administration (FDA); Company-recognized authoritative pharmacology compendia; or published peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of evinacumab-dgnb (Evkeeza) outside of the Dosing and Frequency Requirements listed in this policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of this drug. If the member’s dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the utilization management activities. The Company reserves the right to conduct postpayment review and audit procedures for any claims submitted for evinacumab-dgnb (Evkeeza).

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.
The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the service.
When coverage of evinacumab-dgnb (Evkeeza) is requested outside of the Dosing and Frequency Requirements listed in this policy, the prescribing professional provider must supply documentation (i.e., published peer-reviewed literature) to the Company that supports this request.

Guidelines

There is no Medicare coverage determination addressing evinacumab-dgnb (Evkeeza); therefore, the Company policy is applicable.

BENEFIT APPLICATION

Subject to the applicable Evidence of Coverage, evinacumab-dgnb (Evkeeza) is covered under the medical benefits of the Company’s Medicare Advantage products when the medical necessity criteria and Dosing and Frequency Requirements listed in this medical policy are met.

For Medicare Advantage members, certain drugs are available through either the member's medical benefit (Part B benefit) or pharmacy benefit (Part D benefit), depending on how the drug is prescribed, dispensed, or administered. This medical policy only addresses instances when evinacumab-dgnb (Evkeeza) is covered under a member's

medical benefit (Part B benefit). It does not address instances when evinacumab-dgnb (Evkeeza) is covered under a member's pharmacy benefit (Part D benefit).

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Evinacumab-dgnb (Evkeeza) was approved by the US Food and Drug Administration (FDA) on February 11, 2021, as an adjunct to other low-density lipoprotein cholesterol (LDL-C)–lowering therapies for the treatment of adult and pediatric individuals, aged 12 years and older, with homozygous familial hypercholesterolemia (HoFH). On March 21, 2023, the FDA expanded the indication to treat adult and pediatric individuals, aged 5 years and older, with HoFH. The safety profile of evinacumab-dgnb (Evkeeza) in pediatric individuals aged 5 to 11 years was similar to the safety profile in adults and pediatric individuals aged 12 years and older, with the additional adverse reaction of fatigue. The safety and effectiveness in pediatric individuals younger than 5 years of age have not been established.

Description

Homozygous familial hypercholesterolemia (HoFH) is a rare, severe, genetic disorder of lipid metabolism caused by variation(s) in the *LDLR* gene, which leads to low or absent hepatic clearance of LDL cholesterol (LDL-C) from the circulation, resulting in LDL-C levels usually above 400 mg/dL. HoFH affects approximately 1 in 300,000 individuals. Individuals with HoFH are at an increased risk of premature atherosclerotic cardiovascular disease; heart attacks and/or mortality before age 30 may occur if they are not aggressively treated. Another characteristic of HoFH is xanthomas, firm nodules occurring in the skin or tendons, caused by cholesterol build-up. Treatment consists of HMG-CoA Reductase Inhibitors "statins", ezetimibe (Zetia), proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors, or apheresis. Apheresis and some statins are at this time the only US Food and Drug Administration (FDA)–approved treatment options for children 5 to 10 years of age. The FDA has approved the other therapies for older children or adults, due to safety and efficacy established in studies.

Evinacumab-dgnb (Evkeeza) is a recombinant human monoclonal antibody that binds to and inhibits angiopoietin-like protein 3 ($ANGPTL_3$). $ANGPTL_3$ slows the function of certain enzymes that break down fats in the body. Evinacumab-dgnb (Evkeeza) blocks $ANGPTL_3$, allowing faster breakdown of fats that leads to a reduction in LDL-C, HDL-C, triglycerides (TG), total cholesterol (TC), and apolipoprotein B and TG. Note: The effects of evinacumab-dgnb (Evkeeza) on cardiovascular morbidity and mortality have not been determined. The recommended dose of evinacumab-dgnb (Evkeeza) is 15 mg/kg administered by intravenous (IV) infusion over 60 minutes once monthly (every 4 weeks).

PEER-REVIEWED LITERATURE

SUMMARY
Adults

The safety and effectiveness of evinacumab-dgnb (Evkeeza) was evaluated in a multicenter, double-blind, randomized, placebo-controlled trial in 65 individuals with HoFH. The diagnosis of HoFH was determined by genetic testing (documented variant in two *LDLR* alleles OR the presence of homozygous or compound heterozygous variants in apolipoprotein B [*APOB*] or *PCSK9*) OR demonstrated in individuals with untreated TC greater than 500 mg/dL, LDL-C greater than or equal to 70 mg/dL, and triglycerides less than 300 mg/dL and either a presence of cutaneous or tendinous xanthomas before 10 years of age or documentation of TC greater than 250 mg/dL in both parents. Patients who had compound heterozygosity or homozygosity for variants in the gene encoding LDL receptor adaptor protein-1 (*LDLRAP1*) were also eligible. Participants were receiving other lipid-lowering therapies at baseline: 94% were on a statin (77% high-intensity statin), 75% on ezetimibe, 77% on a PCSK9 inhibitor, 25% on lomitapide, 34% undergoing apheresis. Participants were on the following combination therapies at baseline: 44% were receiving a three-drug regimen (ezetimibe, PCSK9 inhibitor, and statin), 11% on a four-drug regimen (ezetimibe, lomitapide, PCSK9 inhibitor, and statin), and 63% were on at least three lipid-lowering therapies.

Participants received either evinacumab-dgnb (Evkeeza) 15 mg/kg IV every 4 weeks (N=43) or placebo (N=22) for 24 weeks. After the double-blind treatment period, 64 of 65 participants entered a 24-week open-label extension period in which all participants received evinacumab-dgnb (Evkeeza) 15 mg/kg IV every 4 weeks. The primary efficacy endpoint was percent change in LDL-C from baseline to Week 24. At Week 24, those who received evinacumab-dgnb (Evkeeza) experienced LDL-C reduction from baseline of 47.1% compared with an increase of 1.9% in those on placebo (P<0.0001). Adverse events occurred in 66% of individuals receiving evinacumab-dgnb (Evkeeza) versus 81% for placebo; adverse events did not lead to discontinuation in either group. Serious adverse events occurred in

two individuals (5%) in the evinacumab-dgnb (Evkeeza) group (urosepsis and suicide attempt); both patients recovered.

Pediatric Individuals Aged 12 to 17 Years

At Week 24, evinacumab-dgnb (Evkeeza) reduced LDL-C by 73% in one pediatric individual, compared with a 60% reduction in the individual on placebo.

In an open-label extension study, 13 pediatric individuals with HoFH (12–17 years of age) received 15 mg/kg IV of evinacumab-dgnb (Evkeeza) every 4 weeks as an adjunct to other lipid-lowering therapies for a median of 33 weeks. Evinacumab-dgnb (Evkeeza) reduced LDL-C by 52% in the nine individuals who completed treatment and had a lipid assessment at Week 24. The researchers stated that overall, the effect of evinacumab-dgnb (Evkeeza) on lipid parameters in pediatric individuals with HoFH was generally similar to that seen in adults with HoFH.

Pediatric Individuals Aged 5 to 11 Years

The safety and effectiveness of evinacumab-dgnb (Evkeeza) in pediatric individuals aged 5 to 11 years was evaluated a multicenter, three-part, single-arm, open-label trial performed in 14 individuals with HoFH (Wiegman et al., 2024). At baseline, individuals had LDL-C greater than 130 mg/dL despite aggressive lipid-lowering therapies. Part A was a phase 1b, single-dose, open-label, 16-week study that assessed the safety, pharmacokinetics, and pharmacodynamics of evinacumab in six individuals. Part B evaluated the efficacy of evinacumab-dgnb (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). At Week 24, evinacumab-dgnb (Evkeeza) reduced LDL-C by 48%. Part C is an ongoing, phase 3, 48-week open-label extension study with a 24-week follow-up period, designed to assess the long-term safety and efficacy of evinacumab, which includes all 20 individuals from both parts A and B.

OFF-LABEL INDICATION
There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

References

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)
E78.01 Familial hypercholesterolemia

HCPCS Level II Code Number(s)
J1305 Injection, evinacumab-dgnb, 5mg

Revenue Code Number(s)

N/A

Coding And Billing Requirements

Policy History

Revisions From MA08.133c:

09/16/2024	This version of the policy will become effective 09/16/2024. This policy has been updated to communicate the expanded coverage for pediatric individuals 5 to 11 years of age with homozygous familial hypercholesterolemia (HoFH). Additionally, the treated low-density lipoprotein cholesterol (LDL-C) levels were updated from greater than or equal to 70 mg/dL to greater than or equal to 100 mg/dL in accordance with the American College of Cardiology Guidelines.

Revisions From MA08.133b:

05/07/2024	This policy has been reissued in accordance with the Company's annual review process.
02/08/2023	This policy has been reissued in accordance with the Company's annual review process.
03/23/2022	This policy has been reissued in accordance with the Company's annual review process.
10/01/2021	This policy has been identified for the HCPCS code update, effective 10/01/2021. The following HCPCS codes have been **removed** from this policy: C9079 Injection, evinacumab-dgnb, 5 mg J3590 Unclassified biologic The following HCPCS code has been **added** to this policy: J1305 Injection, evinacumab-dgnb, 5mg

Revisions From MA08.133a:

07/01/2021	This policy has been identified for the HCPCS code update, effective 07/01/2021. The following HCPCS code has been **added** to this policy: C9079 Injection, evinacumab-dgnb, 5 mg The following HCPCS code has been **removed** from this policy: C9399 Unclassified drugs or biologicals

Revisions From MA08.133:

05/24/2021	The following new policy has been developed to communicate the Company's coverage criteria for evinacumab-dgnb (Evkeeza).

Version Effective Date:
09/16/2024
Version Issued Date:
09/16/2024

Version Reissued Date:
N/A