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Coverage Policy Number **IP0128**

Evinacumab

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for evinacumab-dgnb (Evkeeza) injection for intravenous use.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Evinacumab-dgnb (Evkeeza) is considered medically necessary when the following are met:

1. **Homozygous Familial Hypercholesterolemia (HoFH).** Individual meets **ALL** of the following criteria:
    A. 5 years of age or older
    B. Individual meets **ONE** of the following:
        i. Has genetic confirmation of biallelic pathogenic alleles in the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* gene

ii. Has an untreated low-density lipoprotein (LDL-C) level of at least 500 mg/dL (prior to treatment with any antihyperlipidemic agent) AND meets **ONE** of the following:
    a. Individual had clinical manifestations of HoFH before 10 years of age
    b. Both parents of the individual had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia (HeFH) (for example, both parents had an untreated LDL-C level of at least 190 mg/dL and/or an untreated total cholesterol level greater than 250 mg/dL)
iii. Has a treated LDL-C level of at least 300 mg/dL AND meets **ONE** of the following: Treated refers to after therapy with at least one antihyperlipidemic agent. Some examples of antihyperlipidemic agents include statins (e.g., atorvastatin, rosuvastatin, lovastatin, simvastatin, pravastatin), ezetimibe, a PCSK9 inhibitor (e.g., Praluent [alirocumab injection for subcutaneous use]), Evkeeza (evinacumab-dgnb injection for intravenous use), or Juxtapid (lomitapide capsules).
    a. Had clinical manifestations of HoFH before 10 years of age
    b. Both parents of the individual had untreated LDL-C levels or total cholesterol levels consistent with HeFH (for example, both parents had an untreated LDL-C of at least 190 mg/dL and/or an untreated total cholesterol greater than 250 mg/dL)

C. Individual meets **ONE** of the following criteria:
    i. Documented contraindication per FDA label to statin therapy
    ii. Individual meets **BOTH** of the following:
        a. Documented trial of **ONE** high-intensity statin therapy (for example, atorvastatin 40 mg daily or higher; rosuvastatin tablets 20 mg daily or higher [as a single-entity or as a combination product]) for at least 8 continuous weeks
        b. Low-density lipoprotein cholesterol level after this treatment remains at 70 mg/dL or higher
D. Use is adjunctive to diet and maximally tolerated statin therapy (unless contraindicated or intolerant [Appendix A])
E. Documentation of **ONE** of the following:
    i. Has had an inadequate response (LDL-C remains at 70 mg/dL or higher) to **ONE** proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor for at least 8 continuous weeks
    ii. Has a contraindication per FDA label, significant intolerance, or is not a candidate for **ONE** proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor
    iii. Known to have two LDL-receptor negative alleles
    iv. Individual is 5 to 9 years of age upon initiation of therapy
F. The medication is prescribed by or in consultation with a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders

Dosing. Up to 15 mg/kg administered by intravenous infusion no more frequently than once every 4 weeks

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Evinacumab-dgnb (Evkeeza) is considered medically necessary for continued use when the above medical necessity criteria are met **AND** there is documentation of beneficial response.

Authorization Duration

Initial approval duration is up to 12 months.
Reauthorization approval duration is up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven including the following (this list may not be all inclusive):

1. **Heterozygous Familial Hypercholesterolemia (HeFH).** The safety and effectiveness of Evkeeza have not been established in patients with hypercholesterolemia who do not have HoFH, including those with HeFH.[1]

2. **Hyperlipidemia.** Although data are available, the prescribing information for Evkeeza states that the safety and efficacy of Evkeeza have not been established in patients with other forms of hypercholesterolemia.[1,3]
   Note: This is not associated with homozygous familial hypercholesterolemia and is referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.

Coding / Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

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

Background

OVERVIEW

Evkeeza, an angiopoietin-like 3 inhibitor, is indicated as an adjunct to other low-density lipoprotein cholesterol (LDL-C) lowering therapies for the treatment of homozygous familial hypercholesterolemia (HoFH) in patients ≥ 5 years of age.[1]

In the pivotal trial that led to approval of Evkeeza, patients were receiving additional medications to lower LDL-C levels such as statins (94% [77% of patients at high-intensity statin doses]), a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor (77%), ezetimibe (75%), and Juxtapid® (lomitapide capsules). Although some Phase II data are available,[3] the safety and effectiveness of Evkeeza have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH).[1] The effects of Evkeeza on cardiovascular (CV) morbidity and mortality have not been determined.

Disease Overview

Familial hypercholesterolemias, which include HeFH and HoFH, encompass a group of genetic defects that cause severe elevations in LDL-C levels, as well as other lipid parameters.[4,5] HoFH impacts approximately 1 in 300,000 to 1,000,000 persons. The condition is most commonly due to impaired functionality of the low-density lipoprotein (LDL) receptor which leads to a low or absence of clearance of LDL-C from the circulation. Currently known causes of familial hypercholesterolemia include mutations in the LDL receptor, apolipoprotein B, or PCSK9 genes. Clinical manifestations of HoFH are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma. Patients with familial hypercholesterolemia may have physical findings such as tendon or cutaneous xanthomas, which may occur in childhood. Individuals with familial hypercholesterolemia are at very high risk of atherosclerotic cardiovascular disease (ASCVD) at a premature age. Most guidelines recommended LDL-C targets of < 100 mg/dL for adults and < 70 mg/dL for adults with ASCVD or other risk factors. Statins are the initial treatment for familial hypercholesterolemia. For patients with HoFH, high-intensity statin therapy is recommended, with ezetimibe added as well. Therapy with a PCSK9

inhibitor (e.g., Repatha® [evolocumab subcutaneous injection]) is usually the next step. Other non-statin therapies can be considered (e.g., colesevelam tablets or oral suspension, niacin). Combination therapy is required for most patients. LDL apheresis is recommended in certain circumstances. Patients with HoFH should be managed by a lipid specialist. Table 1 provides some of the diagnostic criteria to establish a diagnosis of HoFH. The diagnosis of HoFH can be done by genetic or clinical criteria.

Table 1. Criteria for the Diagnosis of HoFH.[5]

- Genetic confirmation of two mutant alleles at the LDLR, Apo B, PCSK9 or LDLRAP1 gene locus; OR
- An untreated LDL-C > 500 mg/dL* or treated LDL-C ≥ 300 mg/dL* together with either 1) cutaneous or tendon xanthoma before the age of 10 years OR 2) untreated elevated LDL-C levels consistent with heterozygous FH in both parents.

HoFH – Homozygous familial hypercholesterolemia; LDLR – Low-density lipoprotein receptor; Apo B – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9; LDLRAP1 – Low-density lipoprotein receptor adaptor protein 1; LDL-C – Low-density lipoprotein cholesterol; * These cited LDL-C levels are only indicative and lower levels, especially in children or in untreated patients do not exclude HoFH; FH – Familial hypercholesterolemia.

Guidelines

Evkeeza is addressed in the American College of Cardiology Expert Consensus Decision Pathway on the role of non-statin therapies for LDL-C lowering in the management of ASCVD risk (2022).[6] Several guidelines provide strategies for managing familial hypercholesterolemia, including HoFH.[5,7]

- **American College of Cardiology (2022):** Specialized therapies, one of which includes Evkeeza, may be needed to control LDL-C in certain patients (e.g., those with HoFH) who have had an inadequate response to statins, with or without ezetimibe, and PCSK9 inhibitors.[6] Evkeeza should be administered under the care of a lipid specialist.
- **American Heart Association/American College of Cardiology (2018):** In patients with severe primary hypercholesterolemia (LDL-C ≥ 190 mg/dL) begin high-intensity statin therapy.[7] 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).
- **European Atherosclerosis Society (2014):** A position paper by this organization recommends lipid-lowering therapy be initiated as soon as possible with LDL-C targets for HoFH of < 100 mg/dL in adults or < 70 mg/dL in adults with clinical ASCVD.[5] Statins are a mainstay of therapy and are often used in combination with other agents such as ezetimibe. Other agents can be alternatives as well (e.g., Juxtapid). Lipoprotein apheresis may also be considered.

Appendix A

Statin Intolerance

Statin intolerance occurs when an individual is unable to continue to use a statin, either because of the development of a side effect or because of evidence on a blood test that certain markers of liver function or muscle function (creatine kinase) are sufficiently abnormal to cause concern. The intolerance can be either partial (for example, only some statins at some doses) or complete (for example, all statins at any dose).

The most common presentation of statin intolerance is myalgia (for example, muscle aches, pains, weakness, or cramps), which can occur in up to 15% of individuals treated with statins. In most cases, the symptoms are mild and are rarely associated with myositis (muscle inflammation) and markers of muscle injury (creatine kinase). Of note, the symptoms are completely reversible shortly after the statin is stopped. Serious muscle damage or rhabdomyolysis associated with statin treatment is extremely rare, for instance, occurring in 1 in 23 million individuals with prescriptions for atorvastatin. Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]). Mild to moderate increases in creatine kinase may occasionally be seen in

patients taking statins who have no muscle-related side effects, but this should not be grounds to stop statin therapy.[7]

References

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