Drug Coverage Policy

Effective Date.....8/15/2024
Coverage Policy Number.....IP0128
Policy Title.....Evkeeza

Homozygous Familial Hypercholesterolemia – Evkeeza

- Evkeeza® (evinacumab-dgnb intravenous infusion – Regeneron)

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. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. 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.

Cigna Healthcare Coverage Policy

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. 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], Praluent® [alirocumab subcutaneous injection]) is usually the next step. Juxtapid can be added onto maximal lipid-lowering therapy and Evkeeza may be considered. Combination therapy is required for most patients. LDL apheresis is recommended in certain circumstances. The diagnosis of HoFH can be done by genetic or clinical criteria.[5] An untreated LDL-C (> 400 mg/dL) is suggestive of HoFH. Patients may have cutaneous or tendon xanthomas before 10 years of age and/or untreated elevated LDL-C levels consistent with HeFH in both parents. In the digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH.

Guidelines
Guidelines provide strategies for managing familial hypercholesterolemia, including HoFH, and mention the role of Evkeeza.[5,6]

- **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]
- **European Atherosclerosis Society (2023):** Clinical guidance by this organization recommends lipid-lowering therapy be initiated with high-intensity statin therapy and ezetimibe.[5] A PCSK9 inhibitor can be added as well. If not at LDL-C goals, other agents can be alternatives as well (e.g., Juxtapid, Evkeeza). Lipoprotein apheresis may also be considered. The goal is to reduce LDL-C to < 115 mg/dL in children and adolescents, < 70 mg/dL in adults if no major ASCVD risk factors are present, and < 55 mg/dL if patients have ASCVD or major ASCVD risk factors.

Medical Necessity Criteria

Evkeeza is considered medically necessary when the following are met:

FDA-Approved Indication

1. **Homozygous Familial Hypercholesterolemia.** Approve for 1 year if the patient meets ONE of the following (A or B):
   A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, and iv):
      i. Patient is ≥ 5 years of age; AND
      ii. Patient meets ONE of the following (a, b, or c):
         a) Patient has phenotypic confirmation of homozygous familial hypercholesterolemia; OR
            Note: Examples include pathogenic variants at the low-density lipoprotein receptor (LDLR), apolipoprotein B (apo B), proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene.
         b) Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level > 400 mg/dL AND meets ONE of the following [(1) or (2)]:
            Note: Untreated refers to prior to therapy with any antihyperlipidemic agent.
            (1) Patient had clinical manifestations of homozygous familial hypercholesterolemia before the age of 10 years; OR
               Note: Clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma.
            (2) At least one parent of the patient had untreated LDL-C levels or total cholesterol levels consistent with familial hypercholesterolemia; OR
               Note: An example of familial hypercholesterolemia is an untreated LDL-C level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL.
         c) Patient has a treated LDL-C level ≥ 300 mg/dL AND meets ONE of the following [(1) or (2)]:
            Note: 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 (i.e., Repatha [evolocumab subcutaneous injection, Praluent [alirocumab subcutaneous injection]), or Juxtapid (lomitapide capsules).
            (1) Patient had clinical manifestations of homozygous familial hypercholesterolemia before the age of 10 years; OR
               Note: Examples of clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma.
            (2) At least one parent of the patient had untreated LDL-C levels or total cholesterol levels consistent with familial hypercholesterolemia; AND
               Note: An example of familial hypercholesterolemia is an untreated LDL-C ≥ 190 mg/dL and/or an untreated total cholesterol > 250 mg/dL.
      iii. Patient meets ONE of the following (a or b):
         a) Patient meets ALL of the following [(1), (2), and (3)]:
            (1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single entity or as a combination product]); AND
            (2) Patient has tried one high-intensity statin along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND
            (3) Low-density lipoprotein cholesterol level after this treatment regimen remains ≥ 70 mg/dL; OR
         b) Patient has been determined to be statin intolerant by meeting ONE of the following [(1) or (2)]:
            (1) Patient experienced statin-related rhabdomyolysis; OR
               Note: 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]).

(2) Patient meets ALL of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination product); AND

(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as a combination product) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND
Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Patient meets ONE of the following (a, b, or c):

a) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has tried one PCSK9 inhibitor for ≥ 8 continuous weeks; AND
Note: Examples of PCSK9 inhibitors include Repatha (evolocumab subcutaneous injection) and Praluent (alirocumab subcutaneous injection).

(2) The LDL-C level after this PCSK9 inhibitor therapy remains ≥ 70 mg/dL; OR

b) Patient is known to have two LDL-receptor negative alleles; OR

c) Patient is 5 to 9 years of age; OR

B) Patient Currently Receiving Evkeeza. Approve if according to the prescriber, the patient has experienced a response to therapy.
Note: Examples of a response to therapy include decreasing LDL-C, total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Evkeeza for this specific indication through Cigna, review under criteria for Initial Therapy. If the patient is restarting therapy with Evkeeza, Initial Therapy criteria must be met.

Dosing. Approve 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.

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

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Heterozygous Familial Hypercholesterolemia.** 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 HoFH and is referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated LDL-C levels.

Coding Information

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

References

1. Evkeeza® intravenous infusion [prescribing information]. Tarrytown, NY: Regeneron; March 2023.
2. Raal FJ, Rosenson RS, Reeskamp LF, et al, for the ELIPSE HoFH investigators. Evkeeza for homozygous familial hypercholesterolemia. *N Engl J Med*. 2020;383(8):711-720.
3. Rosenson RS, Burgess LJ, Ebenbichler CF, et al. Evkeeza in patients with refractory hypercholesterolemia. *N Engl J Med*. 2020;383(24):2307-2319.
4. Raal FJ, Hovingh GK Catapano AL. Familial hypercholesterolemia treatments: guidelines and new therapies. *Atherosclerosis*. 2018;277:483-492.
5. Cuchel M, Raal FJ, Hegele RA, et al. 2023 update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J*. 2023;44:2277-2291.
6. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *J Am Coll*. 2022;80(14):1366-1418.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Updated** the title of the policy from Evinacumab to Homozygous Familial Hypercholesterolemia – Evkeeza. **Homozygous Familial Hypercholesterolemia:** Clarified "Initial Therapy" versus "Currently Receiving Evkeeza" criteria and added additional examples of what is considered a response to therapy; Removed "Use is adjunctive to diet and maximally tolerated statin therapy [unless	8/15/2024

	contraindicated or intolerant"; Updated the statin intolerance criteria, to clearly define what is considered statin intolerant, with notes and examples also included. For Initial Therapy, the specialist physician requirement was removed. The requirement that the patient has had genetic confirmation by two mutant alleles at the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9, or low-density lipoprotein receptor adaptor protein 1 gene locus was changed to state that the patient has phenotypic confirmation of homozygous familial hypercholesterolemia and the above examples moved to a Note. The diagnostic criterion which stated that the patient has an untreated low-density lipoprotein cholesterol level > 500 mg/dL was changed to > 400 mg/dL. The criterion (which is in two places [those with an untreated low-density lipoprotein cholesterol level > 400 mg/dL and a treated low-density lipoprotein cholesterol level ≥ 300 mg/dL]) that both parents of the patient had untreated low-density lipoprotein cholesterol levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia was changed to state that at least one parent of the patient had untreated low-density lipoprotein cholesterol levels or total cholesterol levels consistent with familial hypercholesterolemia. The related Note that "An example of heterozygous familial hypercholesterolemia in both parents would be if both had an untreated low-density lipoprotein cholesterol level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL" was changed to state "An example of familial hypercholesterolemia is an untreated low-density lipoprotein cholesterol level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL."	

The policy effective date is in force until updated or retired.