PRIOR AUTHORIZATION POLICY

POLICY: Homozygous Familial Hypercholesterolemia – Evkeeza Prior Authorization Policy
- Evkeeza® (evinacumab-dgnb intravenous infusion – Regeneron)

REVIEW DATE: 02/23/2022

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 adults and pediatric patients ≥ 12 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 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 (apo 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]) 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 not addressed in guidelines. Several guidelines provide strategies for managing familial hypercholesterolemia, including HoFH.

- **American Heart Association/American College of Cardiology (2018)**: In patients with severe primary hypercholesterolemia (LDL-C ≥ 190 mg/dL) begin high-intensity statin therapy.[6] 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.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Evkeeza. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Evkeeza, as well as the monitoring required for adverse events and long-term efficacy, approval requires Evkeeza to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: None required.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Evkeeza is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Homozygous Familial Hypercholesterolemia.** Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
   - **A)** Patient is ≥ 12 years of age; AND
   - **B)** Patient meets one of the following (i, ii or iii):
     - **i.** Patient has had genetic confirmation of two mutant alleles 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 locus; OR
     - **ii.** Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level > 500 mg/dL AND meets one of the following (a or b):
       Note: Untreated refers to prior to therapy with any antihyperlipidemic agent.
       - **a)** Patient had clinical manifestations of homozygous familial hypercholesterolemia (HoFH) before the age of 10 years; OR
         Note: Clinical manifestations of HoFH are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma.
       - **b)** Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia (HeFH); OR
         Note: An example of HeFH in both parents would be if both had an untreated LDL-C level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL.

iii. Patient has a treated low-density lipoprotein cholesterol (LDL-C) level ≥ 300 mg/dL AND meets one of the following (a or b):
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).
- **a)** Patient had clinical manifestations of homozygous familial hypercholesterolemia (HoFH) before the age of 10 years; OR
  Note: Examples of clinical manifestations of HoFH are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma.
- **b)** Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia (HeFH); AND
  Note: An example of HeFH in both parents would be if both had an untreated LDL-C ≥ 190 mg/dL and/or an untreated total cholesterol > 250 mg/dL.

C) Patient meets one of the following criteria (i or ii):
- **i.** Patient meets all of the following criteria (a, b, and c):
  - **a)** Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin tablets ≥ 20 mg daily [as a single-entity or as a combination product]); AND
  - **b)** Patient has tried one high-intensity statin along with ezetimibe (as a single entity or as a combination product) for ≥ 8 continuous weeks; AND
  - **c)** The low-density lipoprotein cholesterol (LDL-C) level after this treatment regimen remains ≥ 70 mg/dL; OR
- **ii.** Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
  - **a)** 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]).
  - **b)** Patient meets all of the following criteria [(1), (2), and (3)]:
    - **(1)** 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).
    - **(2)** The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND
    - **(3)** When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) 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.

D) Patient meets one of the following (i or ii):
- **i.** Patient meets both of the following (a and b):
  - **a)** Patient has tried one proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor for ≥ 8 continuous weeks; AND
    Note: Examples of PCSK9 inhibitors include Repatha (evolocumab subcutaneous injection) and Praluent (alirocumab subcutaneous injection).
  - **b)** The low-density lipoprotein cholesterol (LDL-C) level after this PCSK9 inhibitor therapy remains ≥ 70 mg/dL; OR
- **ii.** Patient is known to have two LDL-receptor negative alleles; AND

E) Medication is prescribed by or in consultation with a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Evkeeza is not recommended in the following situations:

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.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Evkeeza® intravenous infusion [prescribing information]. Tarrytown, NY: Regeneron; February 2021.
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, Bruckert E, Ginsberg HN, et al, for the European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolemia. Homozygous familial hypercholesterolemia: new insights and guidance for clinicians to improve detection and clinical management. A positive paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J*. 2014;35:2146-2157.
6. Grundy SM, Stone NJ, Bailey AL, et al. ACC/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082-e1143. Available at: https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000625. Accessed on February 15, 2022.

HoFH – Homozygous familial hypercholesterolemia; LDL-C – Low-density lipoprotein cholesterol; HeFH – Heterozygous familial hypercholesterolemia.