evinacumab-dgnb (Evkeeza™)

Policy # 00751
Original Effective Date: 08/09/2021
Current Effective Date: 08/14/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider evinacumab-dgnb (Evkeeza™)‡ for the treatment of homozygous familial hypercholesterolemia (HoFH) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for evinacumab-dgnb (Evkeeza) will be considered when the following criteria are met:

Initial Authorization: (Patient must meet I, II, III, IV, V, and VI)

I. Patient is ≥ 5 years of age; AND

II. Patient is adherent to any medications required for therapy prior to receiving authorization for evinacumab-dgnb (Evkeeza); AND
*(Note: This specific patient selection criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

III. evinacumab-dgnb (Evkeeza) will be used along with a maximally tolerated statin [in those who are not considered statin intolerant (see below for statin intolerance)] AND a maximally dosed proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor, such as Repatha®‡ (evolocumab) or Praluent®‡ (alirocumab), unless the patient has two LDL-receptor negative alleles, AND generic ezetimibe 10 mg daily; AND

IV. Patient meets one of the following criteria which confirms the diagnosis of HoFH (Patient must meet A, B, or C):
    A. 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

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B. Patient has an untreated (i.e. prior to therapy with any anti-hyperlipidemic agent) low-density lipoprotein cholesterol (LDL-C) level > 500 mg/dL AND meets one of the following criteria (i or ii):
   i. Patient had clinical manifestations of HoFH (i.e. cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma) before the age of 10 years; OR
   ii. Both parents of the patient had untreated (i.e. prior to therapy with any anti-hyperlipidemic agent) LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia (HeFH); OR
   iii. (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.)

C. Patient has a treated (i.e. therapy with at least one anti-hyperlipidemic agent) LDL-C level ≥ 300 mg/dL AND meets one of the following criteria (i or ii):
   i. Patient had clinical manifestations of HoFH (i.e. cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma) before the age of 10 years; OR
   ii. Both parents of the patient had untreated (i.e. prior to therapy with any anti-hyperlipidemic agent) 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.)

V. Patient meets one of the following criteria (A or B):
   A. Patient meets all of the following criteria (i, ii, and iii)
      i. Patient has tried one high-intensity maximum daily dose statin therapy (i.e., generic atorvastatin ≥ 80 mg daily; generic rosuvastatin ≥ 40 mg daily [as a single-entity or as a combination product]) for ≥ 12 continuous weeks OR patient has tried a maximally tolerated stable daily dose statin of any potency for ≥ 12 continuous weeks if proof is given that a high potency maximum daily dose statin was not well tolerated [as a single-entity or as a combination product]); AND
      *(Note that the 12 week timeframe is an additional company requirement and will be denied as not medically necessary** if not met)*

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ii. Patient has taken the statin along with generic ezetimibe 10 mg daily (as a single entity or as a combination product) for ≥ 12 continuous weeks, unless the patient is statin intolerant (defined below), then generic ezetimibe 10 mg daily without a statin should be taken for ≥ 12 continuous weeks; AND
*(Note that the 12 week timeframe is an additional company requirement and will be denied as not medically necessary** if not met)*

iii. Patient's LDL-C level after this treatment regimen remains ≥ 70 mg/dL or ≥100 mg/dL based on "high risk" or "very high risk" classifications of the patient; OR

B. Patient has been determined to be statin intolerant by meeting the following criteria (i and ii):

i. Patient's LDL-C level remains ≥ 70 mg/dL or ≥100 mg/dL based on "high risk" or "very high risk" classifications of the patient due to statin intolerance; AND

ii. Patient meets all of the following criteria [(1), (2), and (3)]:

1. Patient was unable to tolerate at least 2 different statins. [The inability to tolerate one statin will be accepted if the patient experienced rhabdomyolysis or clinically-significant myonecrosis secondary to a statin. Rhabdomyolysis/myonecrosis is considered to be a muscle breakdown with signs and symptoms such as muscle pain, weakness, tenderness ALONG WITH either: a.) acute renal failure or myoglobinuria AND elevated creatine kinase levels (e.g., ≥ 10 times the upper limit of normal) OR b.) elevated creatine kinase levels (e.g., ≥ 10 times the upper limit of normal) alone]; AND
2. Patient's intolerance was associated with confirmed, intolerable statin-related adverse effects [e.g., skeletal related muscle symptoms (myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness])]; AND
3. Patient's symptoms or biomarker changes resolved or showed significant improvement on dose decrease or discontinuation; AND

VI. Patient meets one of the following criteria (A, B, or C):

A. Patient meets both of the following criteria (i and ii):

i. Patient has tried a PCSK9 inhibitor for ≥ 12 continuous weeks at the FDA approved maximum dose for HoFH; AND

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(Note: Examples of PCSK9 inhibitors at their maximum dose include Repatha (evolocumab) 420 mg once every 2 weeks and Praluent (alirocumab) 150 mg once every 2 weeks)
*(Note that the 12 week timeframe is an additional company requirement and will be denied as not medically necessary** if not met)*

ii. Patient's LDL-C level after the max PCSK9 inhibitor HoFH dosing regimen remains ≥ 70 mg/dL or ≥100 mg/dL based on "high risk" or "very high risk" classifications of the patient; OR

B. Patient is known to have two LDL-receptor negative alleles; OR
C. Patient is 5 to 9 years of age.

Re-authorization: (Patient must meet I and II)

I. Patient previously met the initial criteria and received an approval for evinacumab-dgnb (Evkeeza); AND
II. Patient has achieved clinically significant LDL-C lowering AND is adherent to evinacumab-dgnb (Evkeeza)
*(Note that the re-authorization criteria are additional company requirements and will be denied as not medically necessary** if not met)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of evinacumab-dgnb (Evkeeza) when the member has not tried the required pre-requisite medications for a timeframe of at least 12 weeks to be **not medically necessary.****

Based on review of available data, the Company considers the use of evinacumab-dgnb (Evkeeza) when the re-authorization criteria are NOT met to be **not medically necessary.****

Based on review of available data, the Company considers the use of evinacumab-dgnb (Evkeeza) when the patient is not compliant with their cholesterol lowering regimen to be **not medically necessary.****

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of evinacumab-dgnb (Evkeeza) when patient selection criteria are not met (except those listed above as **not medically necessary****) to be **investigational.***

Background/Overview

Evkeeza is an ANGPTL3 (angiopoietin-like 3) inhibitor indicated 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 (HoFH). 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). Evkeeza's inhibition of ANGPTL3 leads to reduction in LDL-C, HDL-C, and triglycerides (TG). Evkeeza 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. Evkeeza's blockade of ANGPTL3 lowers TG and HDL-C by rescuing LPL and EL activities, respectively. Evkeeza is supplied in 345 mg and 1,200 mg single-dose vials and is dosed at 15 mg/kg administered intravenously (IV) once monthly over 60 minutes. It should be noted that the safety and efficacy of Evkeeza have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH). The effects of Evkeeza on cardiovascular morbidity and mortality have not been determined.

Hypercholesterolemia/Treatment Guidelines

Approximately 30% of the United States population has elevated LDL-C (low density lipoprotein cholesterol). There is also a subset of hypercholesterolemia, known as familial hypercholesterolemia, which can affect nearly 1 in 300 individuals. Familial hypercholesterolemia can further be broken down into homozygous and heterozygous forms of familial hypercholesterolemia. The homozygous form is by far the rarest with an estimated incidence of 1 in 1,000,000 individuals. HoFH is most commonly due to impaired functionality of the LDL receptor, which leads to a low or absence of clearance of LDL-C from the circulation. Genetic testing is available to determine whether or not an individual has familial hypercholesterolemia, however

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clinical signs/symptoms are often a more practical method of diagnosing this condition. Known mutations causing HoFH are located in the LDL receptor, apolipoprotein B (apo B), or proprotein convertase subtilisin kexin type 9 (PCSK9) genes. Patients with HoFH may have physical findings including tendon or cutaneous xanthomas coupled with elevated LDL-C levels (>500 mg/dL [untreated] and >300 mg/dL [treated]). The gold standard for the treatment of elevated LDL-C levels is a statin given along with ezetimibe (Zetia) to provide the greatest amount of LDL-C lowering. Statin products also have proven cardiovascular outcomes. Next steps in therapy for HoFH patients would include the PCSK9 inhibitors, Praluent and Repatha, which also have cardiovascular outcomes.

The American College of Cardiology (ACC)/American Heart Association (AHA) treatment guidelines no longer set treatment goals for hyperlipidemia. The guidelines instead emphasize the appropriate intensity of statin therapy to reduce cardiovascular risk in patients who will benefit. These guidelines also emphasize the benefits of LDL-C reduction. The National Lipid Association does set LDL-C treatment goal levels for patients at various risk stratifications. Those with clinical atherosclerotic cardiovascular disease would fall into the "very high risk" category and would therefore be treated to an LDL-C of less than 70 mg/dL. Patients with familial hypercholesterolemia could fall into either the "very high risk" or "high risk" categories, based on their patient characteristics and would therefore have a treatment goal of less than 70 mg/dL or 100 mg/dL (respectively). Risk stratification (per the National Lipid Association) is as follows:

Risk Classifications:

Very High Risk:

I. Clinical ASCVD (atherosclerotic cardiovascular disease)[#]; OR
II. Diabetes Mellitus with ≥2 other Major ASCVD risk factors^ OR diabetes mellitus with end organ damage [e.g., increased albumin/creatinine ratio (≥30mg/g), chronic kidney disease, or retinopathy]

High Risk:

I. ≥ 3 major ASCVD risk factors^; OR
II. Diabetes Mellitus with 0-1 other Major ASCVD risk factors^; OR
III. Chronic kidney disease (GFR ≤44 mL/min); OR
IV. LDL-C ≥190 mg/dL (untreated); OR
V. Quantitative risk score reaching the high risk threshold (one of the following)

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A. ≥10% using Adult Treatment Panel III Framingham risk score for hard coronary heart disease (CHD, MI, or CHD death); OR
B. ≥15% using the 2013 Pooled Cohort Equations for hard ASCVD (MI, stroke, or death from CHD or stroke); OR
C. ≥45% using the Framingham long-term CVD (MI, CHD death or stroke) risk calculator

#Clinical ASCVD (includes one of more of the following):

I. Myocardial infarction (MI) or other acute coronary syndrome (ACS)
II. Coronary or other revascularization procedure
III. Transient ischemic attack
IV. Ischemic stroke
V. Atherosclerotic peripheral arterial disease (ABI of <0.90)
VI. Other documented atherosclerotic diseases in symptomatic patients such as
    A. Clinically significant coronary atherosclerosis diagnosed by coronary angiography, stress test, stress echocardiography, or myocardial perfusion imaging
    B. Renal atherosclerosis
    C. Aortic aneurysm secondary to atherosclerosis
    D. Carotid plaque (≥50% stenosis)

^ASCVD Risk factors:

I. Age
    A. Male ≥45 years
    B. Female ≥55 years
II. Family history of early CHD (MI, death, or coronary revascularization procedure)
    A. <55 years of age in a male first degree relative or
    B. <65 years of age in a female first degree relative
III. Current cigarette smoking
IV. High blood pressure (≥140/≥90 mm Hg) or on a blood pressure medication)
V. Low HDL-C
    A. Male <40 mg/dL
    B. Female <50 mg/dL

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Treatment Goals:

Risk	LDL-C Treatment Goal
Very High Risk	<70 mg/dL
High Risk	<100 mg/dL

Statin Intolerance

Statins have been associated with muscle-related adverse effects such as myalgia (e.g., muscle aches, soreness, stiffness, or tenderness), myopathy (muscle weakness), and/or myositis (muscle inflammation). Although the incidence is variable, muscle adverse effects are reported in around 5% of patients receiving statins, but may be due to other causes (e.g., excessive exercise, other medical conditions [hypothyroidism], non-statin medications). It is advisable to assess for drug interactions as well as to check vitamin D levels and thyroid function status. Rhabdomyolysis, which is uncommon with statin therapy, is a severe muscle-related adverse effect that results in muscle breakdown associated with muscle-related symptoms (e.g., muscle pain, weakness, tenderness) along with acute renal failure and elevated creatine kinase [CK] levels (myonecrosis). In patients with statin-related muscle adverse events, symptoms may not re-occur if the patient switches to a different statin therapy. Pravastatin and fluvastatin appear to have much less intrinsic muscle toxicity than other statins and could be considered for those who had statin related intolerable muscle symptoms.

In 2014, the NLA Statin Intolerance Panel published an update. It was stated that most statin intolerance is due to myalgia. The strongest evidence at present for statin intolerance in a population is that myalgia appears but then remits with withdrawal but reoccurs with re-challenge. The incidence of statin intolerance is widely variable. The Panel states that statins are among the safest medications available. The Panel does advise that due to statin benefits, it is safe to recommend a patient continue statin therapy even when some degree of statin intolerance is present, if the patient can reasonably tolerate the statin. A pivotal trial with Praluent called ODYSSEY ALTERNATIVE defined statin intolerance as the inability to take at least two different statins due to muscle-related adverse effects, of which one statin was administered at the lowest approved starting dose. Data also suggests that many patients who are re-challenged with statin therapy after an adverse event may be able to tolerate statin therapy long-term. Of note, in the ODYSSEY ALTERNATIVE trial with Praluent, 69.8% of patients who were considered statin intolerant were treated with atorvastatin 20 mg daily and completed the double-blind 24-week portion of the trial. This suggests that re-challenge

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with a statin in those purported to be statin intolerant is reasonable and may lead to successful use of a statin therapy.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Evkeeza is indicated 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. It should be noted that the safety and efficacy of Evkeeza have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH). The effects of Evkeeza on cardiovascular morbidity and mortality have not been determined.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

ELIPSE-HoFH was a multicenter, double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of Evkeeza compared to placebo in 65 patients with HoFH. 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.

Patients were on a background of other lipid-lowering therapies, including maximally tolerated statins, ezetimibe, PCSK9 inhibitor antibodies, lomitapide, and lipoprotein apheresis. The mean 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.

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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 cross over from placebo to Evkeeza and was maintained in patients who remained on Evkeeza for 48 weeks.

In an open-label trial (Trial 2), 13 pediatric patients with HoFH (aged 12 to 17 years) received 15 mg/kg of Evkeeza given intravenously 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 Evkeeza on lipid parameters in pediatric patients aged 12 to 17 years with HoFH was generally similar to that seen in adults with HoFH.

Trial R1500-CL-17100 (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. In Part B, the mean LDL-C at baseline was 264 mg/dL.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%).

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07/01/2021	Medical Policy Committee review
07/14/2021	Medical Policy Implementation Committee approval. New policy.
09/30/2021	Coding update
07/07/2022	Medical Policy Committee review
07/13/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/06/2023	Medical Policy Committee review
07/12/2023	Medical Policy Implementation Committee approval. Updated the age for use from 12 years to 5 years to align with the FDA approval update.

Next Scheduled Review Date: 07/2024

Coding

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Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J1305
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment,

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would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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