# Drug Monograph

Drug Name: **Evkeeza™ (evinacumab-dgnb) Solution for Injection**
Drug Class: **Angiopoietin-Like Protein 3 Inhibitor**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

## Executive Summary

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|---|---|
| **Purpose:** | The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use. |
| **Dosage Forms:** | Evkeeza is available in single-dose vials containing either 345 mg/2.3 mL (150 mg/mL) or 1200 mg/8 mL (150 mg/mL) solution for injection. |
| **Manufacturer:** | Manufactured by: Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591. |
| **Summary of Findings:** | The efficacy of Evkeeza was established in a multicenter, randomized, double-blind, placebo-controlled Phase III trial (ELIPSE-HoFH) in patients 12 years of age and older with homozygous familial hypercholesterolemia for 24 weeks. Patients were randomized to receive either Evkeeza 15 mg/kg intravenous (IV) infusion every 4 weeks (n= 43) or placebo (n= 22). Patients were able to continue current lipid-lowering therapies during the trial. The primary efficacy endpoint was percentage change in calculated LDL-C from baseline to week 24. The least squares 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). |
| **Status Recommendation:** | ☐ Prior Authorization (PA) Required ☐ Open Access<br>☐ Clinical Edit ☒ PDL |
| **Type of PA Criteria:** | ☐ Increased Risk of ADE ☒ Non-Preferred Agent<br>☐ Appropriate Indications ☐ No PA Required |

## Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

## Introduction [1,2,3]

Homozygous familial hypercholesterolemia (HoFH) is a rare autosomal dominant disorder that is life-threatening if left untreated. The typical patient will not survive past 30 years of age without intensive medical and lifestyle interventions. HoFH is typically characterized by a marked elevation in circulating low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC), xanthomas and advanced, premature atherosclerotic cardiovascular disease. Symptoms are consistent with ischemic heart disease, peripheral vascular disease, cerebrovascular disease, aortic stenosis as well as tendonitis. HoFH is diagnosed by genetic testing, physical examination, lipid panel analysis as well as a review of the patient's family history. Secondary causes of hypercholesterolemia are often ruled out during this process. The goal of therapy is to reduce the risk of coronary heart disease (CHD) or any other type of CHD-equivalent condition as early as possible. It is estimated that HoFH affects about 1 in 160,000 to 1 in 300,000 people worldwide with about 1,300 people being affected in the United States.

## Dosage Form [4]

Evkeeza is available in both 345 mg/2.3 mL (150 mg/mL) and 1200 mg/8 mL (150 mg/mL) single-dose vials for injection.

## Manufacturer [4]

Manufactured by: Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591.

## Indication(s) [4,5]

Evkeeza is indicated for use as an adjunct therapy to other LDL-C lowering therapies for the treatment of adult and pediatric patients, aged 12 years and older, with HoFH.

## Clinical Efficacy [3,4,5,6]

Evkeeza is an angiopoietin-like protein 3 (ANGPTL3) inhibitor. ANGPTL3 which is primarily expressed on the liver, plays a viable role in the regulation of lipid metabolism through the inhibition of lipoprotein lipase (LPL) and endothelial lipase (EL). The inhibition of ANGPTL3 leads to a reduction of 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. The reduction in TG and HDL-C are due to LPL and EL activities being left intact through ANGPTL3 inhibition.

 

Pharmacokinetics:

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| **Absorption** | $C_{max}$ (end of infusion): 157 mg/L |
| **Distribution** | $V_d$: 4.8 L |
| **Metabolism** | Mechanism largely unknown; (possible route is through degradation into small peptides and amino acids via catabolic pathways, similar to endogenous IgG) |
| **Excretion** | • High concentrations: primarily a non-saturable proteolytic pathway<br>• Low concentrations: primarily via non-linear, saturable ANGPTL3 target-mediated pathway.<br>• Evkeeza is not likely to undergo renal excretion. |
| **Half-life** | Based upon Evkeeza concentrations and is not constant. |

Clinical Trials Experience:

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| **STUDY 1 DESIGN (ELIPSE-HoFH)** | Multicenter, double-blind, randomized, placebo-controlled, parallel-group Phase 3 trial |
| **INCLUSION CRITERIA** | ● Subjects 12 years of age and older<br>● Diagnosis of functional HoFH<br>● If undergoing LDL apheresis, must have started LDL apheresis at least 3 months prior to screening and must have been on a stable weekly or every other week schedule and/or stable settings for at least 8 weeks<br>● Willing to consistently maintain his/her usual low fat or heart healthy diet for the duration of the trial |
| **EXCLUSION CRITERIA** | ● LDL-C level < 70 mg/dL at screening visit<br>● Background medical Lipid Modifying Therapy (if applicable) that has not been stable before the screening visit<br>● Lipid apheresis schedule/ apheresis settings that have not been stable for at least 8 weeks before screening visit<br>● Use of nutraceuticals or over-the-counter therapies known to affect lipids, at a dose/ amount that has not been stable for at least 4 weeks prior to screening visit<br>● Any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins<br>● Newly diagnosed (within 3 months prior to randomization visit) diabetes mellitus or poorly controlled (HbA1c >9%) diabetes<br>● History of cardiovascular disease (i.e. MI, unstable angina leading to hospitalization, coronary artery bypass graft surgery, percutaneous coronary intervention, uncontrolled cardiac arrhythmia, carotid surgery or stenting, valve replacement surgery) within 3 months prior to screening visit<br>● Endovascular procedure or surgical intervention for peripheral vascular disease within 3 months prior to screening visit<br>● Stroke or transient ischemic attack within 3 months prior to screening visit<br>● Pregnant or breastfeeding women<br>● Sexually active women of child bearing potential (WOCBP) who are unwilling to practice a highly effective birth control method prior to the initial dose, during the trial and for 24 weeks after taking the last dose of study drug<br>● Men who are sexually active with WOCMP and are unwilling to consistently use condoms during the study drug treatment period and for 24 weeks after the last dose of study drug regardless of vasectomy status |

<table>
<tr><td>TREATMENT REGIMEN</td><td>During the 24 week treatment period, patients were randomized to receive Evkeeza 15 mg/kg IV every 4 weeks (N= 43) or placebo (N= 22). After the double-blind treatment period, 64 of the 65 patients entered a 24 week open-label extension period in which all patients received Evkeeza 15 mg/kg IV every 4 weeks.</td></tr>
<tr><td>RESULTS</td><td>The primary efficacy endpoint was percent change in calculated LDL-C from baseline to Week 24.
<table>
<tr><th></th><th>LDL-C</th><th>ApoB</th><th>Non-HDL-C</th><th>TC</th><th>TG[a]</th><th>HDL-C[a]</th></tr>
<tr><td>Baseline (mean), mg/dL (N=65)</td><td>255</td><td>171</td><td>278</td><td>322</td><td>124</td><td>44</td></tr>
<tr><td>LS Mean: EVKEEZA (N=43)</td><td>-47%</td><td>-41%</td><td>-50%</td><td>-47%</td><td>-55%</td><td>-30%[b]</td></tr>
<tr><td>LS Mean: Placebo (N=22)</td><td>+2%</td><td>-5%</td><td>+2%</td><td>+1%</td><td>-5%</td><td>+1%[b]</td></tr>
<tr><td>LS Mean Difference from Placebo (95% CI)</td><td>-49% (-65 to -33)</td><td>-37% (-49 to -25)</td><td>-52% (-65 to -39)</td><td>-48% (-59 to -39)</td><td>-50% (-66 to -35)</td><td>-[b]</td></tr>
</table>
[a] Neither TG nor HDL-C were pre-specified in the hypothesis testing<br>
[b] Mean percent change, based on safety population (EVKEEZA, n=44; placebo, n=20); HDL-C is presented for completeness but was not an efficacy endpoint that was statistically analyzed. One subject in the placebo group discontinued the study before Week 24. The treatment difference and 95% confidence interval (CI) were estimated using a mixed model repeated measures analysis.
<ul>
<li>At Week 24, using the least squares mean treatment difference between Evkeeza and placebo in mean percentage change in LDL-C from baseline was -49% (95% confidence interval: -65% to -33%; p <0.0001).</li>
<li>Significant reductions were observed in secondary endpoints included apolipoprotein B (ApoB) and non-high-density lipoprotein cholesterol (non-HDL-C) as compared to placebo.</li>
<li>The open-label arm of the extension phase (Week 24 to Week 48) showed the observed LDL-C reduction from baseline being similar in patients who crossed over from placebo to Evkeeza and was maintained in patients who remained on Evkeeza for 48 weeks.</li>
</ul></td></tr>
<tr><td>SAFETY</td><td>Discussed in the Adverse Effects section below.</td></tr>
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## Contraindications (4)

- Hypersensitivity to evinacumab or any component in Evkeeza.

## Warnings and Precautions (4)

- Breast feeding
- Infusion-related reactions: (pruritis, pyrexia, muscular weakness, nausea, nasal congestion)
- Possible anaphylaxis
- Pregnancy (fetal harm may occur as seen in animal reproductive studies)

 

## Adverse Effects [4]

| Most common, ≥3% | Evkeeza (N =81) % | Placebo (N=54) % |
|---|---|---|
| Nasopharyngitis | 16 | 13 |
| Flu-like symptoms | 7 | 6 |
| Infusion-related reactions | 7 | 4 |
| Dizziness | 6 | 0 |
| Nausea | 5 | 2 |
| Rhinorrhea | 5 | 0 |
| Pain in extremity | 4 | 0 |
| Asthenia | 4 | 0 |

## Drug Interactions [4]

- No known drug interactions

## Dosage and Administration [4]

Evkeeza is administered via IV infusion of 15 mg/kg over 60 minutes once monthly (every 4 weeks).

*Lipid lower therapies (statins, ezetimibe, PCSK9 inhibitors, lomitapide, and/ or apheresis) may be continued while taking evinacumab.

## Cost

| Generic Name | Brand Name | Manufacturer | Dose | Cost**/ Year |
|---|---|---|---|---|
| Evinacumab | Evkeeza™ | Regeneron | 15 mg/kg by IV infusion over 60 minutes once monthly (every 4 weeks) | $448,200 for an 80 kg patient |

** Wholesale Acquisition Cost

## Conclusion

Evkeeza is the first FDA-approved treatment that binds to and blocks the function of ANGPTL3. Currently, Evkeeza is only indicated as an adjunct therapy to other LDL-C lowering therapies in patients 12 years of age and older with HoFH. In the Phase III clinical trial ELIPSE- HoFH, adding Evkeeza to other lipid therapies resulted in a reduction of LDL-C by 49% vs +2% in placebo patients at 24 weeks. At this time, safety and efficacy of Evkeeza has not yet been established in patients who have hyperlipidemia from other causes including Heterozygous Familial Hypercholesterolemia. A Phase II clinical trial is currently underway evaluating a subcutaneous formulation for this potential indication though.

## Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL) as non-preferred.

 

## References


1. "What is Homozygous Familial Hypercholesterolemia (HoFH)." *The FH Foundation.org.*, 2021 URL. https://thefhfoundation.org/familial-hypercholesterolemia/what-is-homyzygous-familial-hypercholesterolemia. Accessed 10 May 2021.
2. July M, Khardori R. (2021, April 9). Familial Hypercholesterolemia. *eMedicine.* Retrieved May 10, 2021 from https://emedicine.medscape.com/article/121298-overview.
3. IPD Analytics. Cardiovascular: Dyslipidemia Class Management. Accessed May 11, 2021. Available at URL: https://secure.ipdanalytics.com/User/Pharma/RxStrategy/Page/f6099cc7-17e0-49ce-86bc-162ec47024a5#section-group-184523
4. Evkeeza™ (evinacumab-dgnb) [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2021 Feb.
5. Evkeeza: Drug Information. Lexi-Drugs. Wolters Kluwer Clinical Drug Information Inc.
6. National Library of Medicine. (2018, January – 2020, March). *Efficacy and Safety of Evinacumab in Patients with Homozygous Familial Hypercholesterolemia*. Identifier: NCT03399786. https://clinicaltrials.gov/ct/show/NCT03399786



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