NEW DRUG APPROVAL

Brand Name	Evkeeza™
Generic Name	evinacumab-dgnb
Drug Manufacturer	Regeneron Pharmaceuticals, Inc.

New Drug Approval

FDA Approval Date: February 11, 2021

Review Designation: Orphan

Type of Review: Biologic License Application (BLA): 761181

Dispensing Restrictions: Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Familial hypercholesterolemia (FH) is a common life-threatening genetic condition that causes high cholesterol. Untreated, FH leads to early heart attacks and heart disease. People with FH have a high amount of low-density lipoprotein (LDL) or "bad cholesterol" due to a mutation in one of the genes that controls the way cholesterol is cleared by the body. As a result, cholesterol accumulates in the bloodstream and can ultimately build up in the walls of the arteries. Cholesterol build up in the artery wall is called hardening of the arteries, or atherosclerosis, and can lead to problems such as heart attacks and strokes in young adults and even children.

There are two forms of FH:

- Heterozygous Familial Hypercholesterolemia (HeFH) and
- Homozygous Familial Hypercholesterolemia (HoFH).

HoFH is an ultra-rare form of high cholesterol that affects about 1 in 300,000 people. It is an inherited defect in how the body recycles LDL (bad) cholesterol and causes LDL levels in the blood to remain very high.
FH can be inherited from one parent (heterozygous FH), or, in rare instances, from both (homozygous FH). People with HoFH can have very high LDL cholesterol levels, and some may need bypass surgeries before adulthood. If left untreated, people with HoFH develop atherosclerosis before the age of 20 years and generally do not survive past 30 years. Men with FH get coronary heart disease up to 10 to 20 years earlier than the general population. In women, coronary heart disease appears up to 20 to 30 years earlier than in the general population. About 30% of untreated women with HoFH will have a heart attack before 60 years of age.

Efficacy

ELIPSE HoFH (NCT03399786) was a multicenter, double-blind, randomized, placebo-controlled trial that evaluated the efficacy and safety of Evkeeza™ compared with 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 were randomized 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.

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Table 1. ELIPSE HoFH (NCT03399786): Study Design Summary	

Study Population	• 65 patients 12 years of age and older with homozygous familial hypercholesterolemia (HoFH); 53 patients (82%) had a genetically confirmed diagnosis of HoFH
	• **Mean age:** 42 years (range, 12 to 75 years)
	  ○ 54% female; 74% White, 15% Asian, 3% Black, 8% other or not reported
	• **Mean baseline LDL-C:** 260 mg/dL (evinacumab), 247 mg/dL (placebo)
	  ○ At baseline, 94% of patients were on a statin, 77% on a PCSK9 inhibitor, 75% on ezetimibe, 25% on lomitapide, and 34% on apheresis

Interventions	• Patients were randomized 2:1 to receive one of the following:
	  ○ Evkeeza 15 mg/kg IV every 4 weeks (n = 43) plus other lipid-lowering therapies
	  ○ Lipid-lowering therapies alone (placebo, n = 22)

Endpoints	• **Primary:** Percent change in LDL-C from baseline to Week 24 • **Key secondary outcomes:** Percent change from baseline in ApoB, non-HDL-C, and TC
Efficacy and Safety Results	• 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 [CI]: −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 crossed over from placebo to Evkeeza and was maintained in patients who remained on Evkeeza for 48 weeks. • At Week 24, the LS mean treatment difference between Evkeeza and placebo in mean percent change from baseline in ApoB, non-HDL-C, and TC was −37%, −52%, and −48%, respectively (*P* <0.0001 for all). • Adverse events during the treatment period occurred in 66% of the patients in the evinacumab group and 81% of those in the placebo group. No patients discontinued either evinacumab or placebo because of an adverse event: there were no deaths. Antidrug antibodies did not develop during the treatment period in any patients. • Serious adverse events during the treatment period occurred in 2 patients (5%) in the evinacumab group and were reported as urosepsis and a suicide attempt. Both patients recovered. • No cardiovascular events were reported in either group during the double-blind treatment period. An influenza-like illness was reported in 5 of 44 patients (11%) in the evinacumab group and in no patients in the placebo group. • An increase in the level of either alanine aminotransferase or aspartate aminotransferase was reported in 2 of 44 patients (5%) in the evinacumab group and in 2 of 21 patients (10%) in the placebo group, increases that were less than 3 times and 5 times the upper limit of the normal range, respectively. In all cases, elevations were not associated with any symptoms and returned to a normal range while the patients continued to receive either evinacumab or placebo.

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Safety

ADVERSE EVENTS

Common adverse reactions (≥ 5%) were nasopharyngitis, influenza-like illness, dizziness, rhinorrhea, and nausea.

WARNINGS & PRECAUTIONS

- **Serious Hypersensitivity Reactions**: Have occurred with Evkeeza™ in clinical trials. If a serious hypersensitivity reaction occurs, discontinue Evkeeza™, treat according to standard-of-care and monitor until signs and symptoms resolve.
- **Embryo-Fetal Toxicity**: Evkeeza™ may cause fetal harm based on animal studies. Advise patients who may become pregnant of the risk to a fetus. Consider obtaining a pregnancy test prior to initiating treatment with Evkeeza™. Advise patients who may become pregnant to use contraception during treatment and for at least 5 months following the last dose.

CONTRAINDICATIONS

History of serious hypersensitivity reactions to evinacumab-dgnb or to any of the excipients in Evkeeza™.

Clinical Pharmacology

MECHANISMS OF ACTION

Evinacumab-dgnb is a recombinant human monoclonal antibody that binds to and inhibits ANGPTL3. 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). Evinacumab-dgnb inhibition of ANGPTL3 leads to reduction in LDL-C, HDL-C, and triglycerides (TG). Evinacumab-dgnb 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. Evinacumab-dgnb blockade of ANGPTL3 lowers TG and HDL-C by rescuing LPL and EL activities, respectively.

Dose & Administration

ADULTS

15 mg/kg IV infusion over 60 minutes once monthly (every 4 weeks).

PEDIATRICS

If age 12 or older, refer to adult dosing.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None.

HEPATIC IMPAIRMENT

None.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 345 mg/2.3 mL (150 mg/mL) and 1,200 mg/8 mL (150 mg/mL) solution in single-dose vials.