

New Drug Fact Blast

Clinical Services

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| Drug/Manufacturer: | Evkeeza™ (evinacumab-dgnb) [Regeneron] |
| Dosage Formulations: | Injection: 345 mg/2.3 ml (150 mg/ ml) and 1,200 mg/ 8 ml (150 mg / ml) solution in single dose vials. |
| FDA Approval Date: FDB File Date: | FDA: February 11, 2021 FDB: February 21, 2021 |
| Indication: | ANGPTL3 (angiopoietin-like 3) inhibitor indicated as adjunct to other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and pediatric patients aged 12 years and older with homozygous familial hypercholesterolemia (HoFH). |
| Mechanism of Action: | Evinacumab-dgnb is a recombinant monoclonal antibody that binds to and inhibits ANGPTL3. ANGPTL3 is an angiopoietin-like protein expressed in the liver and plays a role in regulation of lipid metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL). By rescuing LPL and EL from ANGPTL3, evinacumab-dgnb lowers LDL-C, HDL-C, and triglycerides (TRG). Evinacumab-dgnb also reduces LDL-C independent of the presence of the LDL receptor (LDL-R) by promoting very-low-density lipoprotein (VLDL) processing and clearance upstream of LDL formation. |
| Dose/ Administration: | 15 mg/kg administered via IV infusion over 60 minutes once monthly (every 4 weeks) |
| Disease State Clinical Highlights: | <ul style="list-style-type: none"> • Homozygous Familial Hypercholesterolemia (HoFH) is an ultra-rare inherited disease that affects 1,300 patients in the U.S. and 1 in 300,000 people worldwide. Patients with HoFH have severely elevated levels of LDL-C, up to 4 times the normal limit (400-1000 mg/dL) without treatment. Known causes of HoFH include gene mutations in the LDL receptor (LDL-R), apolipoprotein B (apo B), or proprotein convertase subtilisin kexin type 9 (PCSK9). Physical findings of HoFH may include premature coronary artery disease (CAD) and tendon and skin xanthomas. These patients can have myocardial infarctions as early as age 10 and the life expectancy may only be 20 years or less. In addition to early diagnosis and intensive treatment, family screening (cascade screening) is required. • Treatment involves early and aggressive lipid-lowering therapies such as high-intensity statins (rosuvastatin, atorvastatin), ezetimibe, bile acid sequestrants, PCSK9 inhibitors (Praluent®, Repatha®), and lipoprotein apheresis. • Patients with HoFH are typically less responsive to standard lipid-lowering therapies including statins and PCSK9 inhibitors. Some patients with HoFH are non-responders to standard lipid-lowering therapies. |
| Drug Clinical Highlights: | <ul style="list-style-type: none"> • Evkeeza is the first FDA-approved treatment that binds to and blocks the function of angiopoietin-like 3 (ANGPTL3) and reduces LDL-C levels in all forms of HoFH including those with little or no LDL receptor activity. • LDL-lowering effects may be measured as early as 2 weeks after initiation of therapy. • Safety and efficacy was evaluated in the Phase 3 ELIPSE (Evinacumab LIPid StudiEs) trial, a multinational, randomized, placebo-controlled, double-blind, parallel-group trial. <ul style="list-style-type: none"> ○ 43 patients were randomized to receive Evkeeza 15mg/kg IV every 4 weeks and 22 patients received placebo. Mean age was 42 years (range 12 to 75), 54% of participants were female. ○ Patients in both arms were on a background of other lipid-lowering therapies, including maximally tolerated statins, ezetimibe, PCSK9 inhibitors, lomitapide, and lipoprotein apheresis. Enrollment was stratified by apheresis status and geological region. |

- 94% of patients were on statins, 75% on ezetimibe, 77% on PCSK9 inhibitors, 22% on lomitapide, and 34% were receiving apheresis.
- Primary endpoint was percent change in LDL-C from baseline at Week 24.
- Secondary endpoints were percent change from baseline in ApoB, non-HDL-C, and TC.

| | LDL-C | ApoB | Non-HDL-C | TC | TG ^a | HDL-C ^a |
|---|----------------------|----------------------|----------------------|----------------------|----------------------|--------------------|
| Baseline (mean), mg/dL (N=65) | 255 | 171 | 278 | 322 | 124 | 44 |
| LS Mean: EVKEEZA (N=43) | -47% | -41% | -50% | -47% | -55% | -30% ^b |
| LS Mean: Placebo (N=22) | +2% | -5% | +2% | +1% | -5% | +1% ^b |
| LS Mean Difference from Placebo (95% CI) | -49% (-65 to -33) | -37% (-49 to -25) | -52% (-65 to -39) | -48% (-59 to -39) | -50% (-66 to -35) | - ^b |

^a Neither TG nor HDL-C were pre-specified in the hypothesis testing

^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.

- The trial reached its primary endpoint at week 24 with patients treated with Evkeeza achieving a 49% on average reduction in LDL-C compared with 2% increase in the placebo group.
- Evkeeza treated patients also experienced 132 mg/dL average reduction in LDL-C compared to 3 mg/dL reduction in the placebo group.
- Significant reductions were observed in secondary endpoints included apolipoprotein B (ApoB) and non-high-density lipoprotein cholesterol (non-HDL-C) as compared to placebo.
- Similar results were seen in difficult to treat patients with little or no LDL-R function (<15% receptor function).
- The reductions in LDL-C with Evkeeza were maintained throughout the double-blind treatment period (week 24) and the open label trial period (through week 48).

Price Per Unit (WAC):

- \$4,668.75 per ml
- 1,200 mg/8 ml vial = \$37,500.00
- 345 mg/2.3 ml vial = \$10,781.25
- For an 80 kg patient, the dose needed is 1,200 mg:
 - \$37,500.00 per once monthly dose
 - \$448,200.00 per year

Therapeutic Alternatives:

- Treatment of HoFH involves a combination of lifestyle changes, medications, and lipoprotein apheresis for severe cases. Apheresis is often indicated once LDL levels reach 300 mg/dl and has been shown to be safe and effective in early childhood.
- Maximally tolerated statins, atorvastatin and rosuvastatin preferred, are considered first line therapy. Addition of ezetimibe, bile acid sequestrants (colesevelam preferred), niacin, PCSK9 inhibitors, and lomitapide are recommended if statin therapy does not achieve adequate LDL lowering.

| Medication | Cost per year | |
|-------------------|---------------|-------|
| Atorvastatin 80mg | \$43.80 | NADAC |
| Rosuvastatin 40mg | \$47.45 | NADAC |
| Ezetimibe | \$54.75 | NADAC |
| Colesevelam | \$1,138.80 | NADAC |
| Niacin | \$350.40 | NADAC |
| Repatha® | \$1,706.28 | NADAC |
| Praluent® | \$2,603.76 | NADAC |
| Juxtapid® | \$536,561.76 | WAC |

- Goals of therapy include:
 - Reducing overall Atherosclerotic Cardiovascular Disease (ASCVD) risk and improve quality of life.
 - Reduce LDL-C by > 50%. Higher risk patients may require more aggressive therapeutic goals (LDL-C <100mg/dl)

Prior Authorization Approval Criteria:

Must meet the following criteria:

Initial Therapy:

- Patient is age 12 or older **AND**
- Diagnosis of Homozygous Familial Hypercholesterolemia (E78.0) confirmed by genetic testing **AND**
- Baseline labs including LDL-C, Apo B, Non-HDL-C, TC, TG, and HDL-C **AND**
- Management/treatment/consultation by or with a lipid disorder specialist
- Trial of a high intensity statin alone or with ezetimibe **OR** documented intolerance to statins (such as statin-induced rhabdomyolysis) **AND** trial of a PCSK9 Inhibitor (Repatha or Praluent)
- Progress notes documenting the need for Evkeeza **AND**
- Prescriber must attest that labs will be monitored during therapy and can be asked for submission at any time during therapy **AND**
- Quantity limit of 1 injection every 4 weeks
- Initial approval for 6 months

Continuation of Therapy:

- Previous prior authorization for initial treatment with Evkeeza and paid claims
- Repeat lipid panel with a shown decrease in lab values from baseline
- Progress notes stating the benefit of treatment including stabilization of disease
- Approve for 1 year

Additional Provider Diagnostic/Monitoring Criteria, if desired:

- Negative pregnancy test and or proof of birth control for female patients during treatment and continue birth control for at least 5 months following last dose.
- History of serious hypersensitivity reactions to evinacumab-dgnb or any of its components in which case the drug should be discontinued
- Adverse reactions (nasopharyngitis, influenza-like illness, dizziness, rhinorrhea, nausea, pain in extremities, asthenia) were greater with Evkeeza over placebo.
- Unwanted immunogenicity - Evkeeza is a therapeutic protein and treatment-emergent antibodies could develop and render the drug ineffective or cause adverse effects (this did not occur in the ELIPSE study)

Implication to State Medicaid Program:

- LOE is to be determined.
- Regeneron has Evkeeza SC, a subcutaneous formulation, in Phase II trials for patients with refractory hypercholesterolemia.

References:

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