



Louisiana

mipomersen (Kynamro[®])

Policy # 00349

Original Effective Date: 04/24/2013

Current Effective Date: 02/21/2018

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.

Note: Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors [alirocumab (Praluent), evolocumab (Repatha)] is addressed separately in medical policy 00472.

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 the use of mipomersen (Kynamro[®])[†] to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol (TC), and non-high density lipoprotein-cholesterol (non HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH) to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility will be considered for mipomersen (Kynamro) when ALL of the following criteria are met:

- Kynamro will be used in conjunction with other treatments for the diagnosis including, but not limited to statins, fibrates, nicotinic acid, ezetimibe, or bile acid sequestrants; AND
- Kynamro is NOT used in combination with a PCSK-9 (proprotein convertase subtilisin kexin type 9) inhibitor (e.g., Repatha^{™†}, Praluent^{®†}); AND;
- Kynamro is NOT used in combination with lomitapide (Juxtapid); AND
- Patient has tried and failed evolocumab (Repatha) 420 mg once monthly after at least 3 months of therapy [unless there is clinical evidence or patient history that suggests evolocumab (Repatha) will be ineffective or cause an adverse reaction to the patient]; AND
*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient has a clinical diagnosis of HoFH, based on the presence of the following:
 - o Patient must have genetic confirmation of two (2) mutant alleles at the low density lipoprotein receptor (LDLR), apoB, PCSK9 or autosomal recessive hypocholesteremia (ARH) adaptor protein gene locus; OR
 - o Patient must have an untreated LDL-C concentration > 500 mg/dL (13 mmol/L); OR
 - o Patient must be compliant with high intensity statin therapy PLUS ezetimibe (Zetia^{®†}), unless patient has a contraindication to taking a statin/ezetimibe (see note below), and the patient has a treated LDL-C ≥ 300 mg/dL (7.76 mmol/L) AND one of the following:
 - Cutaneous or tendonous xanthoma before age of 10 years; OR
 - Untreated LDL-C levels consistent with heterozygous familial hypercholesterolemia (FH) in both parents (> 190 mg/dL).

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Note: "Treated" is defined as having LDL-C levels that are ≥ 300 mg/dL despite at least 90 consecutive days of therapy at the maximum approved or tolerated dose of a high intensity statin [atorvastatin (Lipitor[®])[†] 80mg or rosuvastatin (Crestor[®])[‡] 40mg] PLUS ezetimibe (Zetia). If statin/ezetimibe therapy is contraindicated, reasoning for the contraindication will need to be documented along with documentation of aggressive use of alternate lipid lowering therapy in lieu of statin therapy. (The LDL-C values must come after the consecutive 90 days of lipid lowering therapy, and patient must still be taking the lipid lowering therapy while lab levels are obtained).

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 mipomersen (Kynamro) when patient selection criteria are not met (with the exception of those denoted above as **not medically necessary****) OR for use in conjunction with low density lipoprotein (LDL) apheresis to be **investigational**.*

Based on review of available data, the Company considers the use of mipomersen (Kynamro) in combination with lomitapide (Juxtapid) or PCSK-9 inhibitors to be **investigational**.*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of mipomersen (Kynamro) when the patient has NOT tried and failed evolocumab (Repatha) 420 mg once monthly after at least 3 months of therapy to be **not medically necessary****.

Background/Overview

Mipomersen (Kynamro) is a prescription medicine used along with diet and other lipid-lowering treatments in people with HoFH to reduce:

- LDL ("bad") cholesterol
- TC
- a protein that carries "bad" cholesterol in the blood (apo B)
- non-HDL-C

FH is a genetic disorder characterized by high cholesterol levels, specifically very high levels of LDL in the blood and early cardiovascular disease. Many patients have mutations in the *LDLR* gene that encodes the LDL receptor protein, which normally removes LDL from the circulation, or ApoB, which is the part of LDL that binds with the receptor; mutations in other genes are rare. Patients who have one abnormal copy (are heterozygous) of the *LDLR* gene may have premature cardiovascular disease at the age of 30 to 40. Having two abnormal copies (being *homozygous*) may cause severe cardiovascular disease in childhood. Heterozygous FH is a common genetic disorder, inherited in an autosomal dominant pattern, occurring in 1:500 people in most countries; homozygous FH is much rarer, occurring in 1 in a million births.

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Various lab tests can detect the presence of HoFH. The most common genes that would reflect the presence of HoFH include the LDLR gene, the ApoB gene, and the PCSK9 gene. Lab testing companies such as LabCorp offer a battery of tests to detect mutations in these genes such as the Early-onset Coronary Heart Disease/Familial Hypercholesterolemia: Three-gene Profile (LDLR, APOB, PCSK9) (LDLR/PCSK9-Full Gene Sequencing, APOB-Single Exon Sequencing) **OR** the GeneSeq^{®†}: Cardio Early-onset Coronary Artery Disease/Familial Hypercholesterolemia Profile.

Heterozygous FH is normally treated with statins, bile acid sequestrants or other hypolipidemic agents that lower cholesterol levels. New cases are generally offered genetic counseling. Homozygous FH often does not respond to medical therapy and may require other treatments, including LDL apheresis (removal of LDL in a method similar to dialysis) and occasionally liver transplantation.

Juxtapid and Kynamro were two of the newest drugs to treat this rare condition. However, in mid 2015, Repatha gained U.S. Food and Drug Administration (FDA) approval for the treatment of HoFH at a dose of 420 mg once monthly. Repatha offers an alternative that is much cheaper and more heavily researched than both Juxtapid and Kynamro.

FDA or Other Governmental Regulatory Approval

In January 2013, the FDA approved Kynamro as a subcutaneous injection indicated as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apo B, TC, and non HDL-C in patients with HoFH. Because of the risk of hepatotoxicity, Kynamro is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Kynamro REMS.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Safety data are based on pooled results from four Phase 3, randomized, double-blind, placebo-controlled trials with a total of 390 patients of which 261 patients received weekly subcutaneous injections of 200 mg of Kynamro and 129 patients received placebo for a median treatment duration of 25 weeks (age range 12-81 years, 47% women, 84% Caucasian, 10% Blacks, 3% Asian, 3% other). For the 141 participants who subsequently enrolled in the open-label extension trial, the mean length of study treatment, including exposure to Kynamro in the index study, was 19.8 months and the median was 18.2 months. A total of 41 individuals with HoFH were exposed to Kynamro for at least 6 months and 25 were exposed for at least 12 months.

Eighteen percent of patients on Kynamro and 2% of patients on placebo discontinued treatment due to adverse reactions. The five most common adverse reactions in patients treated with Kynamro that led to

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treatment discontinuation and occurred at a rate greater than placebo were: injection site reactions (5.0%), alanine aminotransferase increased (3.4%), flu-like symptoms (2.7%), aspartate aminotransferase increased (2.3%), and liver function test abnormal (1.5%).

One pivotal, multinational, randomized (2:1), parallel-group, double-blind, placebo-controlled, published, Phase III trial assessed the efficacy of Kynamro in patients with HoFH (n = 51). The mean percent change in LDL-C from baseline to Week 28, the primary efficacy endpoint, was -25% for Kynamro vs. -3% for placebo (P = 0.0003). The effect of Kynamro on cardiovascular morbidity and mortality has not been determined.

References

1. Mipomersen sodium (Kynamro) injection [package insert]. Cambridge, MA: Genzyme Corporation; January 2013.
2. UpToDate. Inherited Disorders of LDL-Cholesterol Metabolism. Accessed 3/2014.

Policy History

Original Effective Date: 04/24/2013

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04/04/2013 Medical Policy Committee review

04/24/2013 Medical Policy Implementation Committee approval. New policy.

05/01/2014 Medical Policy Committee review

05/21/2014 Medical Policy Implementation Committee approval. Included options other than genetic testing in the patient selection criteria.

05/07/2015 Medical Policy Committee review

05/20/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

02/04/2016 Medical Policy Committee review

02/17/2016 Medical Policy Implementation Committee approval. Added requirement for use of Repatha, which is a cheaper alternative that has been studied more than this product. Clarified that Kynamro should not be used with Juxtapid or PCSK9 inhibitors. Treated should reflect a high intensity statin plus Zetia to coincide with more recent practice.

02/02/2017 Medical Policy Committee review

02/15/2017 Medical Policy Implementation Committee approval. Added the generic chemical names for Zetia (ezetimibe), Crestor (rosuvastatin), and Lipitor (atorvastatin). No coverage changes.

02/01/2018 Medical Policy Committee review

02/21/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 02/2019

*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:

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1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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, 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.

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