lomitapide (Juxtapid®)

Policy # 00243
Original Effective Date: 03/20/2013
Current Effective Date: 03/09/2020

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 the use of lomitapide (Juxtapid®)‡ to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), 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 lomitapide (Juxtapid) when all of the following criteria are met:

- Juxtapid will be used in conjunction with other lipid lowering therapy, including, but not limited to statins, nicotinic acid, ezetimibe, bile acid sequestrants, or low-density lipoprotein (LDL) apheresis (where available); AND
- Juxtapid is NOT used in combination with a PCSK-9 (proprotein convertase subtilisin kexin type 9) inhibitor (e.g., Repatha™, Praluent®)‡; 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:
    - Patient must have genetic confirmation of two (2) mutant alleles at the low-density lipoprotein receptor (LDLR), ApoB, PCSK-9 or autosomal recessive hypercholesterolemia (ARH) adaptor protein gene locus; OR

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- Patient must have an untreated LDL-C concentration > 500 mg/dL (13 mmol/L); OR
- Patient must be compliant with high intensity statin therapy PLUS ezetemibe (Zetia®)‡, unless patient has a contraindication to taking a statin/ezetemibe (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 tendinous xanthoma before age of 10 years; OR
  - Untreated LDL-C levels consistent with heterozygous familial hypercholesterolemia (FH) in both parents (> 190 mg/dL).

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 Not Medically Necessary

Based on review of available data, the Company considers the use of lomitapide (Juxtapid) 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.****

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 lomitapide (Juxtapid) when patient selection criteria are not met (with the exception of those denoted above as **not medically necessary****) to be **investigational.***

Based on review of available data, the Company considers the use of lomitapide (Juxtapid) in combination with PCSK-9 (proprotein convertase subtilisin kexin type 9) inhibitors to be **investigational.***

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Background/Overview

Juxtapid is a prescription medicine used along with diet and other lipid-lowering treatments, including LDL apheresis where available, 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.

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 testing options 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.

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. 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.

Juxtapid and Kynamro were two of the newest drugs to treat this rare condition. However, in mid 2015, Repatha gained 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. The manufacturer of Kynamro ceased marketing in August of 2018 and the drug has since been discontinued.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In December 2012, the U.S. FDA approved Juxtapid capsules as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce LDL-C, TC, apo B and non-HDL in patients with HoFH. Because of the risk of hepatotoxicity, Juxtapid is available only through a restricted program called the Juxtapid Risk Evaluation and Mitigation Strategy (REMS) Program.

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, 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.

One single-arm, open-label, 78-week trial has been conducted in 29 patients with HoFH, 23 of whom completed at least one year of treatment. The initial dosage of Juxtapid was 5 mg daily, with titration up to 60 mg daily during an 18-week period based on safety and tolerability. In this trial, the mean age was 30.7 years (range, 18 to 55 years), 16 (55%) patients were men, 25 (86%) patients were Caucasian, 2 (7%) were Asian, 1 (3%) was African American, and 1 (3%) was multi-racial.

Five (17%) of the 29 patients with HoFH that participated in the clinical trial discontinued treatment due to an adverse reaction. The adverse reactions that contributed to treatment discontinuations included diarrhea (2 patients; 7%) and abdominal pain, nausea, gastroenteritis, weight loss, headache, and difficulty controlling INR on warfarin (1 patient each; 3%).

The most common adverse reactions were gastrointestinal, reported by 27 (93%) of 29 patients. Adverse reactions reported by ≥8 (28%) patients in the HoFH clinical trial included diarrhea, nausea,

vomiting, dyspepsia, and abdominal pain. Other common adverse reactions, reported by 5 to 7 (17-24%) patients, included weight loss, abdominal discomfort, abdominal distension, constipation, flatulence, increased alanine aminotransferase (ALT), chest pain, influenza, nasopharyngitis, and fatigue.

The primary efficacy endpoint was percent change in LDL-C from baseline to Week 26. At Week 26, the mean and median percent changes in LDL-C from baseline were -40% (paired t-test $p<0.001$ and -50%, respectively, based on the intent-to-treat population with last observation carried forward (LOCF) for patients who discontinued prematurely. The effect of Juxtapid on cardiovascular morbidity and mortality has not been determined.

References

1. U.S. Food and Drug Administration. Labeling of the drug Lomitapide (Juxtapid). February 2014.
2. UpToDate. Inherited Disorders of LDL-Cholesterol Metabolism. Accessed 3/2014.
3. IPD Analytics. Kynamro. Accessed January 2020.

Policy History

Original Effective Date: 03/20/2013
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03/07/2013	Medical Policy Committee review
03/20/2013	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. Included options other than genetic testing in the patient selection criteria.
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 Juxtapid should not be used with Kynamro or PCSK9 inhibitors. Treated should reflect a high intensity statin plus Zetia to coincide with more recent practice.

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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.
02/07/2019	Medical Policy Committee review
02/20/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/06/2020	Medical Policy Committee review
02/12/2020	Medical Policy Implementation Committee approval. Updated policy to reflect the discontinuation of Kynamro.

Next Scheduled Review Date: 02/2021

*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 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.

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**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.

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

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.