BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 8/16/13**
SECTION: DRUGS	**LAST REVIEW DATE: 5/16/19**
	LAST CRITERIA REVISION DATE: 5/16/19
	ARCHIVE DATE:

JUXTAPID® (lomitapide) oral capsule
KYNAMRO® (mipomersen sodium) subcutaneous injection

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

JUXTAPID® (lomitapide) oral capsule
KYNAMRO® (mipomersen sodium) subcutaneous injection (cont.)

JUXTAPID (LOMITAPIDE) IS AVAILABLE ONLY THROUGH RESTRICTED DISTRIBUTION UNDER A RISK EVALUATION AND MITIGATION STRATEGY (REMS) PROGRAM CALLED JUXTAPID REMS PROGRAM.

Criteria:

- **Criteria for initial therapy:** Juxtapid (lomitapide) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in Cardiology or Endocrinology or is in consultation with a Cardiologist or Endocrinologist

2. Age is 18 years or older

3. A confirmed diagnosis of homozygous familial hypercholesterolemia (HoFH) by **ONE** of the following
   - Genetic testing confirming 2 mutated alleles at LDLR gene or alleles known to affect LDL receptor functionality
   - Skin fibroblast LDL receptor activity < 20% of normal
   - An untreated total cholesterol > 500 mg/dL and triglyceride < 300 mg/dL **and** both parents with documented untreated total cholesterol > 250 mg/dL

4. Individual is currently on and adherent with other lipid lowering treatment

5. Individual is currently on and adherent with a low-fat diet

6. Individual is currently on and adherent with use of a supplement(s) that contains 400 IU vitamin E, 200 mg linoleic acid, 210 mg alpha-linoleic acid (ALA), 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA)

7. **ALL** of the following baseline tests have been obtained before initiation of treatment:
   - Negative pregnancy test, in females of reproductive potential
   - **Per REMS requirement**: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin

8. There are **NO** contraindications:
   - Contraindications include:
     - Pregnancy
     - Simultaneous use of strong to moderate CYP3A4 inhibitors (see Definitions section)
     - Moderate or severe hepatic impairment (Child-Pugh Class B or C)
     - Active liver disease including unexplained persistent abnormal liver function tests

9. Individual does not have hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption

JUXTAPID® (lomitapide) oral capsule
KYNAMRO® (mipomersen sodium) subcutaneous injection (cont.)

10. Will not be used with Praluent (alirocumab) or Repatha (evolocumab) or Kynamro (mipomersin)
11. Women of child bearing potential must be using adequate contraception during therapy
12. Woman who is breast feeding an infant or child should stop breast feeding

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Juxtapid (lomitapide) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in Cardiology or Endocrinology or is in consultation with a Cardiologist or Endocrinologist
2. Individual's condition responded
    - Response is defined as:
        - Achieved and maintains at least a 50% in LDL-C from baseline
3. Individual has been adherent with the medication
4. Individual has been adherent with other lipid lowering therapy
5. Individual has been adherent with low fat diet
6. Individual has been adherent with use of a supplement(s) that contains 400 IU vitamin E, 200 mg linoleic acid, 210 mg alpha-linoleic acid (ALA), 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA)
7. Will not be used with Praluent (alirocumab) or Repatha (evolocumab) or Kynamro (mipomersin)
8. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
    - Contraindications as listed in the criteria for initial therapy section
    - Significant adverse effect such as:
        - Liver toxicity
        - Hepatic steatosis
9. There are no significant interacting drugs

Renewal duration: 12 months

JUXTAPID® (lomitapide) oral capsule
KYNAMRO® (mipomersen sodium) subcutaneous injection (cont.)

KYNAMRO (MIPOMERSEN) IS AVAILABLE ONLY THROUGH RESTRICTED DISTRIBUTION UNDER A RISK EVALUATION AND MITIGATION STRATEGY (REMS) PROGRAM CALLED KYNAMRO REMS PROGRAM.

Criteria:

- **Criteria for initial therapy:** Kynamro (mipomersen) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in Cardiology or Endocrinology or is in consultation with a Cardiologist or Endocrinologist

2. Individual is 18 years of age or older

3. A confirmed diagnosis of homozygous familial hypercholesterolemia (HoFH) documented by **ONE** of the following:
   - Genetic testing confirming 2 mutated alleles at the LDL gene locus
   - An untreated LDL-C of greater than 500 mg/dL (13 mmol/L) **OR** treated LDL-C of greater than 300 mg/dL (7.76 mmol/L) and **ANY** of the following:
     - Cutaneous or tendinous xanthoma before age 10 years
     - Heterozygous familial hypercholesterolemia in both biologic parents with LDL-C greater than 190 mg/dL (4.9 mmol/L) prior to treatment

4. Individual has failed, or is intolerant to, or has a contraindication such that the individual is unable to use Praluent (alirocumab) or Repatha (evolocumab)

5. Will be used as an adjunct to other lipid-lowering medications

6. Will not be used concurrently with Juxtapid (lomitapide) or a PCSK9 inhibitor [e.g., Praluent (alirocumab) and Repatha (evolocumab)]

7. Individual does not have severe renal impairment, clinically significant proteinuria, or on renal dialysis

8. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
   - **Per REMS requirement**: ALT, AST, alkaline phosphatase, and total bilirubin
   - Urinalysis

9. There are **NO** contraindications
   - Contraindications include:
     - Moderate to severe hepatic impairment (Child-Pugh Class B or C)
     - Active liver disease
     - Unexplained persistent elevations of serum transaminases
     - Known hypersensitivity to any components of the product

JUXTAPID® (lomitapide) oral capsule
KYNAMRO® (mipomersen sodium) subcutaneous injection (cont.)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Kynamro (mipomersen) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in Cardiology or Endocrinology or is in consultation with a Cardiologist or Endocrinologist

  2. Individual's condition responded while on therapy
     - Response is defined as achieved and maintains:
       - At least a 20% reduction in LDL-C from baseline

  3. Individual has been adherent with the medication

  4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
     - Contraindications as listed in the criteria for initial therapy section
     - Significant adverse effect such as:
       - Hepatotoxicity
       - Hepatic steatosis

  5. There are no significant interacting drugs

  Renewal duration: 12 months

- Kynamro (mipomersen) for all other indications not previously listed or if above criteria not met is considered ***experimental or investigational*** based upon:

  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

  These indications include, *but are not limited to:*

  - Treatment with dosing or frequency outside the FDA-approved dosing and frequency

JUXTAPID® (lomitapide) oral capsule
KYNAMRO® (mipomersen sodium) subcutaneous injection (cont.)

Description:

Juxtapid (lomitapide) is a microsomal triglyceride transfer protein (MTP) inhibitor indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including low-density lipoprotein (LDL) apheresis where available, 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).

Kynamro (mipomersen) is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis indicated as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apo B, TC and non HDL-C in individuals with HoFH. Apo B is the principal apolipoprotein of LDL and its metabolic precursor, very low density lipoprotein (VLDL).

The safety and effectiveness of Juxtapid (lomitapide) and Kynamro (mipomersen) have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH). The effect of Juxtapid (lomitapide) and Kynamro (mipomersen) on cardiovascular morbidity and mortality has not been determined. Safety and effectiveness in pediatric patients have not established for either agent. The use of Kynamro (mipomersen) as an adjunct to LDL apheresis is not recommended.

Familial hypercholesterolemia (FH) is an inherited disorder categorized as heterozygous (inherited from one parent) or homozygous (inherited from both parents). FH may be caused by mutations in the LDL receptor (LDLR), apolipoprotein B (apo B) and proprotein convertase subtilisin kexin type 9 (PCSK9) genes.

FH is characterized by a high LDL-C level from birth, relatively normal HDL-C and triglycerides, and early-onset coronary heart disease. Findings of FH on physical examination may include arcus corneae (a white ring around the cornea), xanthelasma (sharply demarcated yellowish deposits of fat underneath the skin) and tendon or tuberous xanthomas.

HeFH is more common than HoFH. Individuals with HeFH can present with TC in the range of 350-550 mg/dL. HoFH is more severe than HeFH. Individuals with HoFH can have total cholesterol in the range of 650-1000 mg/dL.

HoFH is a rare inherited disorder in which the body cannot remove LDL-C. HoFH is caused by a loss of function mutations in both alleles of the LDLR gene that encodes the LDLR protein. HoFH may also be considered in an individual with untreated LDL of greater than 500 mg/dL (or an LDL-C 300 mg/dL if on treatment) and one of the following: cutaneous or tendinous xanthomas before age 10, untreated LDL-C of greater than 190 mg/dL in both parents, or evidence of HeFH in both parents.

Individuals with HoFH have markedly impaired removal of LDL-C from the circulation that results from reduced or absent hepatic LDL receptor activity. The hepatic LDL receptor plays a critical role in regulating the concentration of LDL-C in the blood. In the absence of functional LDLR, the uptake of LDL-C from the blood is impaired and concentrations of LDL-C are extremely elevated. As a direct consequence to markedly elevated LDL-C blood levels, individuals with HoFH develop dramatically early and severe atherosclerotic cardiovascular disease (ASCVD) and often, early cardiac-related death. Symptomatic ASCVD often presents during the first 2 decades of life. HoFH affects approximately 1 in 1,000,000 individuals.

JUXTAPID® (lomitapide) oral capsule
KYNAMRO® (mipomersen sodium) subcutaneous injection (cont.)

MTP plays a key role in the assembly and release of apo B-containing lipoproteins, including LDL-C, and inhibition of this protein significantly lowers associated plasma lipid levels. It is an intracellular lipid-transfer protein found in the lumen of the endoplasmic reticulum and is responsible for binding and shuttling individual lipid molecules between membranes. Normal concentrations and function of MTP in the liver and intestine are necessary for the proper assembly and secretion of apo B-containing lipoproteins from the liver and chylomicrons from the intestine. Inhibition of MTP leads directly to decreases in circulating levels of apo B-containing lipoproteins, including LDL-C.

Juxtapid (lomitapide) directly binds and inhibits MTP. Juxtapid (lomitapide) prevents the assembly of apo B-containing lipoproteins in enterocytes and hepatocytes. The result is inhibition of the synthesis of chylomicrons and VLDL. The inhibition of the synthesis of VLDL leads to reduced levels of plasma LDL-C.

Kynamro (mipomersen) is an oligonucleotide inhibitor of apo B-100 synthesis. Apo B is the main component of LDL-C and VLDL, the precursor to LDL-C. Kynamro (mipomersen) binds to the messenger ribonucleic acid (mRNA) of apo B in a sequence-specific manner which results in degradation (RNase H-mediated) or disruption of the mRNA thereby reducing formation of apo B.

Juxtapid (lomitapide) and Kynamro (mipomersen) are only available through a restricted program called JUXTAPID REMS PROGRAM and KYNAMRO REMS PROGRAM respectively. They are only available from certified pharmacies that are enrolled in the program. Providers must be enrolled in the program in order to prescribe Juxtapid (lomitapide) or Kynamro (mipomersen).

Definitions:

Risk Evaluation and Mitigation Strategies (REMS):

Use of Juxtapid or Kynamro is subject to a Risk Evaluation and Mitigation Strategies (REMS) program that requires provider, patient, and dispensing pharmacy be enrolled into the program. Only providers and Pharmacies enrolled into the REMS may prescribe and dispense the drug, respectively, to individuals who are also in the program. A REMS program attempts to manage known or potentially serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) for some drugs to ensure that the benefits of a drug outweigh its risks.

The goal of the Juxtapid REMS and the Kynamro REMS program is to mitigate the risk of hepatotoxicity associated with the use of Juxtapid and Kynamro.

Homozygous familial hypercholesterolemia:

Loss of function mutations in both alleles of the LDLR gene

Heterozygous familial hypercholesterolemia:

Loss of function mutation in one allele of the LDLR gene

JUXTAPID® (lomitapide) oral capsule
KYNAMRO® (mipomersen sodium) subcutaneous injection (cont.)

The Child-Pugh classification system:

	Score: 1 point	**Score: 2 points**	**Score: 3 points**
Serum Albumin (g/dL)	>3.5	3.0 - 3.5	<3.0
Serum Bilirubin (mg/dL)	<2.0	2.0 - 3.0	>3.0
Prothrombin time (seconds)	1 - 4	4 - 6	>6
Ascites	none	moderate	severe
Encephalopathy	none	mild	severe

The three classes and their scores are:
- **Class A** is score 5 – 6: Well compensated
- **Class B** is score 7 – 9: Significant functional compromise
- **Class C** is score >9: Decompensated disease

Inhibitors of Cytochrome P450 metabolism; concurrent use is contraindicated (list is not all inclusive):

3A4 inhibitors:

Strong inhibitors: boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, voriconazole

Moderate inhibitors: amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil

Resources:

Juxtapid package insert, revised by manufacturer 05/2016, reviewed on 06-20-2016, 06-26-17.

Juxtapid package insert, revised by manufacturer 04/2015, reviewed on 06/13/2015

Juxtapid package insert, revised by manufacturer 05/2014, reviewed on 08/13/2014

Juxtapid package insert, revised by manufacturer 12/2012, reviewed on 01/09/2013

Juxtapid package insert, revised by manufacturer 08/2017, reviewed on 07/09/2018, 04/26/19

Kynamro product information accessed 02-08-19 at DailyMed:
https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=774c7847-490b-41d5-9e0e-2baedbc94f62

JUXTAPID® (lomitapide) oral capsule
KYNAMRO® (mipomersen sodium) subcutaneous injection (cont.)

Kastle Therapeutics. An Overview of the Kynamro® Risk Evaluation and Mitigation Strategy (REMS) Program Prescriber Training. Accessed 12/22/2016.

National Organization for Rare Disorders (NORD). NORD Physician Guide to Homozygous Familial Hypercholesterolemia (HoFH). Accessed 12/19/2016.

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:		Dosage Form:
Directions for Use:	Quantity:	Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.