### FDA APPROVED INDICATIONS AND DOSAGE

<table>
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<tr>
<th>Agent</th>
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<th>Dosing (maximum labeled dose) and Administration</th>
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| Juxtapid® (lomitapide) | Adjunct therapy to a low-fat diet and other lipid lowering treatments, including 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). Limitations of Use: The safety and effectiveness of Juxtapid have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH)  | • The recommended starting dose is 5 mg/day, (titrate dose based on acceptable safety/tolerability) after at least 2 weeks increase to 10 mg/day, dose then can be increased every 4 weeks to 20 mg/day, 40 mg/day, and up to the maximum recommended dose of 60 mg/day orally.  
• Patients with end-stage renal disease on dialysis or with baseline mild hepatic impairment should not exceed 40 mg daily.  
• Take with glass of water, without food, at least 2 hours after evening meal. See Table 1 below.  
• Due to reduced absorption of fat-soluble vitamins/fatty acids: Take daily vitamin E, linoleic acid, alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) supplements |
**Kynamro® ( mipomersen )**

Adjunct therapy to lipid lowering medications and diet 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)

Limitations of Use:
The safety and effectiveness of Kynamro have not been established in patients with hypercholesterolemia who do not have HoFH

The effect of Kynamro on cardiovascular morbidity and mortality has not has not been determined

The use of Kynamro as an adjunct to LDL apheresis is not recommended

Recommended dose is 200 mg once weekly as a subcutaneous injection

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**CLINICAL RATIONALE**

Guidelines advise that diagnosis of HoFH can be made on the basis of genetic or clinical criteria. Genetic confirmation of the HoFH includes confirmation of two mutant alleles at the LDL-R, APOB, PCSK9, or LDLRAP1 genes. While genetic testing may provide a definitive diagnosis of HoFH, it is recognized that in some patients, genetic confirmation remains elusive, despite exhaustive investigation; indeed, the existence of additional FH genes cannot be excluded. Historically, HoFH has been most commonly diagnosed on the basis of either an untreated LDL-C plasma concentration >13 mmol/L (>500 mg/dL), or a treated LDL-C concentration of ≥8 mmol/L (≥300 mg/dL), accompanied by the presence of cutaneous or tendon xanthomas before the age of 10 years, or the presence of untreated elevated LDL-C levels consistent with HeFH in both parents.3,4

**Guidelines**

The American Heart Association released a scientific statement for familial hypercholesterolemia that recommended lomitapide or mipomersen may be considered in HoFH patients once a four-drug combination is needed (after rosuvastatin or atorvastatin + ezetimibe + one of the following: PCSK9 inhibitors or colestevolam or other bile acid sequestrant, or niacin combination has been taken by an adherent patient for 3 months and LDL-C is still above goal).6

The European Atherosclerosis Society (EAS) 2014 Consensus Panel clinical guidelines on HoFH state “Early diagnosis of HoFH and prompt initiation of diet and lipid-lowering therapy are critical. Genetic testing may provide a definitive diagnosis, but if unavailable, markedly elevated LDL-C levels together with cutaneous or tendon xanthomas before 10 years, or untreated elevated LDL-C levels consistent with heterozygous FH in both parents, are suggestive of HoFH. We recommend that patients with suspected HoFH are promptly referred to specialist centers for a comprehensive ACVD evaluation and clinical management. Lifestyle intervention and maximal statin therapy are the mainstays of treatment, ideally started in the
first year of life or at an initial diagnosis, often with ezetimibe and other lipid-modifying therapy. As patients rarely achieve LDL-C targets, adjunctive lipoprotein apheresis is recommended where available, preferably started by age 5 and no later than 8 years. The number of therapeutic approaches has increased following approval of lomitapide and mipomersen for HoFH. Given the severity of ACVD, regular follow-up is recommended, including Doppler echocardiographic evaluation of the heart and aorta annually, stress testing and, if available, computed tomography coronary angiography every 5 years, or less if deemed necessary.³

The American Association of Clinical Endocrinologists (AACE) 2017 guidelines state that lomitapide and mipomersen may be useful for individuals with HoFH not responsive to PCSK9 therapy.⁷

The National Organization for Rare Disorders (NORD) states that patients with HoFH are started on statins as soon as the diagnosis is made but these treatments may not be effective alone. Patients with HoFH often require additional treatment strategies including lomitapide, mipomersen and PCSK9 agents. Additional options include LDL apheresis or liver transplantation.⁵

Safety
Both agents have a boxed warning for risk of hepatotoxicity. Both agents can cause elevations in liver enzymes and increase hepatic fat (steatosis). It is recommended to measure ALT, AST, alkaline phosphatase, and total bilirubin prior to initiating therapy and AST and ALT regularly during therapy. Discontinue for clinically significant liver toxicity.¹,²

Both agents also have a REMS program to ensure proper prescribing of the specific agent.¹,²

Contraindications for lomitapide are pregnancy, concomitant use of moderate or strong CYP3A4 inhibitors, and moderate to severe hepatic impairment or active liver disease including unexplained persistent abnormal liver function tests.¹

Contraindications for mipomersen are moderate or severe hepatic impairment or active liver disease, including unexplained persistent elevations of serum transaminases; and known sensitivity to product components.²

REFERENCES
Homozygous Familial Hypercholesterolemia Agents Prior Authorization with Quantity Limit

TARGET AGENTS
Juxtapid® (lomitapide)
Kynamro® ( mipomersen)

INITIAL PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Target agents will be approved when ALL of the following are met:
1. ONE of the following:
   A. The patient has the diagnosis of homozygous familial hypercholesterolemia (HoFH) and ALL of the following:
      i. The patient has a confirmed diagnosis of homozygous familial hypercholesterolemia (HoFH), through ONE of the following:
         1. Genetic confirmation of two mutant alleles at the LDLR, Apo-B, PCSK9, ARH adaptor protein 1/LDLRAP1 gene locus
         OR
         2. History of untreated LDL-C >500 mg/dL (>13 mmol/L) or treated LDL-C ≥300 mg/dL (≥7.76 mmol/L) with ONE of the following:
            a. The patient had cutaneous or tendon xanthoma before age 10 years
            OR
            b. Untreated elevated cholesterol levels consistent with heterozygous FH in both parents [untreated LDL-C >190 mg/dL (>4.9 mmol/L) or untreated total cholesterol greater than 290 mg/dL (>7.5 mmol/L)]
   AND
   ii. ONE of the following:
      1. The patient is on a maximally tolerated statin containing lipid-lowering regimen (i.e. rosuvastatin in combination with ezetimibe OR atorvastatin in combination with ezetimibe)
      OR
      2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL of these therapies (i.e. rosvastatin in combination with ezetimibe AND atorvastatin in combination with ezetimibe)
   AND
   iii. ONE of the following:
      1. The patient has tried with adherence for at least 3 months and had an inadequate response to a PCSK9 inhibitor (e.g. Repatha, Praluent)
      OR
      2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL PCSK9 inhibitors
   AND
   v. If Juxtapid (lomitapide) is requested, the patient is taking daily vitamin E, linolenic acid, alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) supplements
   AND
   vi. If Kynamro (mipomersen) is requested, the patient will NOT be receiving apheresis while on therapy with mipomersen
   OR
   B. The patient has another FDA approved diagnosis
   AND
2. The prescriber is a specialist in the area of the patient’s diagnosis (e.g. cardiologist, endocrinologist, lipid specialist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis

AND

3. The patient does NOT have any FDA labeled contraindications to therapy with the requested agent

AND

4. The requested agent will not be used with any other agent included in the program

AND

5. ONE of the following:
   a. The requested quantity (dose) does NOT exceed the program quantity limit
   OR
   b. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
      AND
      ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose (for the requested indication)
      AND
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

Length of Approval: 12 months for lomitapide
6 months for mipomersen

Renewal Evaluation
Target Agents will be approved for renewal when ALL of the following are met:

1. The patient has been previously approved for therapy with the requested agent through Prime Therapeutics Prior Authorization process

AND

2. The patient has shown clinical benefit with the requested agent

AND

3. ONE of the following:
   A. The patient is on a maximally tolerated statin-containing lipid-lowering regimen (i.e. rosuvastatin in combination with ezetimibe OR atorvastatin in combination with ezetimibe)
   OR
   B. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL of these therapies (i.e. rosuvastatin in combination with ezetimibe AND atorvastatin in combination with ezetimibe)

AND

4. The patient does NOT have any FDA labeled contraindications to the requested agent

AND

5. If Juxtapid (lomitapide) is requested, the patient is taking daily vitamin E, linolenic acid, alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) supplements

AND

6. If Kynamro (mipomersen) is requested, the patient will NOT be receiving apheresis while on therapy with mipomersen

AND

7. The prescriber is a specialist in the area of the patient’s diagnosis (e.g. cardiologist, endocrinologist, lipid specialist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis

AND
8. The requested agent will not be used with any other agent included in the program
   AND
9. ONE of the following:
   a. The requested quantity (dose) does NOT exceed the program quantity limit
      OR
   b. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
         AND
      ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose (for the requested indication)
         AND
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

**Length of approval:** 12 months
Step Therapy Supplement

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT

OBJECTIVE
The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL
The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
      AND
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
      AND
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

   OR

2. The patient’s medication history include the required prerequisite/preferred agent(s) as indicated by:
   a. Evidence of a paid claim(s) within the past 999 days
   OR
   b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

   OR

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: As per program specific criteria