Homozygous Familial Hypercholesterolemia Agents (HoFH) Prior Authorization with Quantity Limit Program Summary

This prior authorization applies to Commercial, GenPlus, NetResults A series, SourceRx and Health Insurance Marketplace formularies.

OBJECTIVE
The intent of the prior authorization (PA) requirement for homozygous familial hypercholesterolemia agents is to encourage appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines and according to dosing recommended in product labeling. Criteria will limit the approved doses for homozygous familial hypercholesterolemia agents to at or below the maximum FDA labeled dose.

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

INITIAL PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
The requested agents will be approved when 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 prescriber has taken baseline labs for ALL of the following:
         1. LDL-C
            AND
         2. Apo B
            AND
         3. Total cholesterol (TC)
            AND
         4. Non-HDL-C
            AND
         5. Triglycerides (TG)

      AND
      ii. 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. Untreated LDL-C >13 mmol/L (>500 mg/dL) or treated LDL-C ≥7.76 mmol/L (≥300 mg/dL) with ONE of the following:
            a. Cutaneous or tendon xanthoma before age 10 years
               OR
            b. Untreated elevated cholesterol levels consistent with heterozygous FH in both parents [untreated total cholesterol >290 mg/dL (7.5 mmol/L) or untreated LDL-C >190 mg/dL]

      AND
      iii. ONE of the following:
         1. The patient is on a maximally tolerated 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. rosuvastatin in combination with ezetimibe AND atorvastatin in combination with ezetimibe)

AND

iv. ONE of the following:

1. The patient has recently tried and failed (adherent for at least the last 3 months) 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, BOTH of the following:

1. The patient will be maintained on a low-fat diet with <20% of calories from fat

AND

2. The patient is receiving a dietary supplement providing approximately 400 IU vitamin E, 210 mg alpha-linolenic acid (ALA), 200 mg linoleic acid, 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA) per day

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

AND

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

AND

4. ONE of the following:

A. The quantity requested (dose) is less than or equal to 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) is less than or equal to the FDA labeled dose

AND

iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit

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

Renewal Evaluation

These agents will be approved for renewal when the following criteria are met:

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

AND

2. The patient has shown a reduction from baseline in at least ONE of the following metrics:

A. LDL-C

B. Apo B
C. Total cholesterol (TC)
D. Non-HDL-C
E. Triglycerides (TG)

AND

3. ONE of the following:
   A. The patient is on a maximally tolerated 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 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 therapy with the requested agent

AND

5. If Juxtapid (lomitapide) is requested, BOTH of the following:
   A. The patient will be maintained on a low-fat diet with <20% of calories from fat
   AND
   B. The patient is receiving a dietary supplement providing approximately 400 IU vitamin E, 210 mg alpha-linolenic acid (ALA), 200 mg linoleic acid, 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA) per day

AND

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

AND

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

AND

8. ONE of the following:
   A. The quantity requested (dose) is less than or equal to 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) is less than or equal to the FDA labeled dose
      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

FDA APPROVED INDICATIONS AND DOSAGE[8,9]

Agent	Indication	Dosing (maximum labeled dose) and Administration
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 effect of Juxtapid on cardiovascular morbidity and mortality has not been determined	• 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.
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 dose is 200 mg once weekly as a subcutaneous injection^

	recommended	

Juxtapid Titration

Table 1: Recommended Regimen for Titrating Dosage

DOSAGE	DURATION OF ADMINISTRATION BEFORE CONSIDERING INCREASE TO NEXT DOSAGE
5 mg daily	At least 2 weeks
10 mg daily	At least 4 weeks
20 mg daily	At least 4 weeks
40 mg daily	At least 4 weeks
60 mg daily	Maximum recommended dosage

CLINICAL RATIONALE

Homozygous familial hypercholesterolemia (HoFH) is a genetic disorder that causes severe elevations in low-density lipoproteins cholesterol (LDL-C) and total cholesterol. Those with HoFH have a very high chance of premature coronary artery disease.[5] Familial hypercholesterolemia is a deficiency or absence of the LDL-C receptors. It can also be caused by mutations of the apolipoprotein B-100 (apoB-100) binding site on LDL-C receptors, PCSK9, and LDLRAP1. Apolipoprotein B (apo B) is a primary component of LDL-C. Apo B is responsible for carrying cholesterol to other tissues. Deficiencies of the LDL-C receptor are often caused by mutations in the *LDLR* gene. The LDLR gene is located on the short arm of chromosome 19.[6] LDL-C receptors are responsible for about 70% of the uptake of circulating LDL-C molecules into the liver.[3] Reductions in the number of LDL-C receptors leads to an accelerated deposition of cholesterol on the walls of arteries. The arteries then harden and narrow and reduce the flow of blood. This reduction in blood flow can lead to cardiovascular diseases like stroke and myocardial infarction. Recent data suggests the prevalence of HoFH in the United States is around 1 case per 160,000 to 250,000 persons, a significant increase from previous estimates.[4,14,15,18] There is no known cure for HoFH. Due to the dysfunction of LDL-C receptors, changes in diet and the use of lipid lowering agents only mildly reduce circulating levels of LDL-C. HoFH normally presents in early childhood. Children and adolescents with a homozygous FH phenotype should receive prompt and aggressive lipid-lowering therapy.[17] Due to the modest reductions in LDL-C levels with diet and stating therapy, even at maximal doses additional treatments are invariably required. These include LDL apheresis, mipomersen, lomitapide, anti-PCSK8 therapy, and liver transplant.

Diagnosis of HoFH can be made on the basis of genetic or clinical criteria. 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 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), and 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."

Guidelines[10-13,18]

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 colesevelam 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).

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, we recommend regular follow-up, 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.

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

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.

Efficacy of Juxtipid[1,8]

The efficacy and safety of lomitapide was evaluated in one pivotal, open label, single arm trial with a total of 29 homozygous familial hypercholesterolemia (HoFH) patients. In this trial, all the participating patients were started on a low dose of lomitapide. Then dose was slowly titrated up every four weeks to maximum tolerated dose. The primary efficacy endpoint in the trial was mean percent change of LDL-C from baseline.

In the pivotal trial, all participants enrolled were over 18 years old. These patients were on stable lipid lowering therapies. The median baseline LDL-C was 336 mg/dL. The primary endpoint, LDL-C was evaluated at weeks 26 and 56. The LDL-C levels were reduced by 40 percent from baseline at week 26, and maintained at 44 percent at week 56 ($P<0.001$). The secondary efficacy parameters for total cholesterol, apolipoprotein B, triglycerides, non-HDL-cholesterol all had statistically significant reductions from observed base line at week 26. The secondary efficacy parameter of lipoprotein A did not show a statistically significant reduction in percent from baseline.

Efficacy of Kynamro[2,9]

The efficacy of mipomersen was evaluated in four placebo controlled, randomized, double blinded placebo controlled trials. The primary endpoint was the percent change in LDL-C from baseline at 28 weeks.

The pivotal trial was ISIS301012-CS5. This trial had 51 participants with clinically or genetically confirmed homozygous familial hypercholesterolemia (HoFH). All participants enrolled were 12 years or older. Patients were stable on low fat diets and lipid lowering therapies. The median baseline LDL-C for the participants was between 402-440 mg/dL. The mean percentage reduction in LDL-C from base line at week 28 was 24.7 percent for the mipomersen arm and 3.3 percent for the placebo arm (p=0.0003). The secondary endpoints of apo B, TC, non-HDL-C, and lipoprotein A all showed statistically significant percent reductions from baseline at week 28. In the pivotal trial 15% of the patient population did not reach at least a 10% decrease in LDL-C from baseline.

Secondary endpoints for pivotal trial included in proposed indication

Secondary endpoint	Time of evaluation	Result mipomersen arm	Result placebo arm	P value
Apolipoprotein (apo B)	28 weeks	26.8 percent	2.5 percent	P<0.0001
Total cholesterol (TC)	28 weeks	21.2 percent	2 percent	P=0.0002
Non-HDL cholesterol	28 weeks	24.5 percent	2.9 percent	P=0.0002
Lipoprotein A	28 weeks	31.1 percent	0.6 percent	P=0.0013

Labeling recommends assessment of efficacy of patients LDL-C level after 6 months to determine if the LDL-C reduction achieved with mipomersen treatment is sufficiently robust to warrant the potential risk of liver toxicity.

Safety[1,2,8,9]
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.

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

A large portion of the lomitapide patient population displayed a 5% or more increase in absolute hepatic fat. Data from the pivotal trial suggests that hepatic fat decreases with the discontinuation of the medication. Given lomitapide's mechanism of action of inhibiting the assembly of apo B-containing lipoproteins, patients may experience fat soluble vitamin deficiencies. Several fat-soluble vitamins were decreased from baseline in patients. The following vitamins should be supplemented daily alpha-linolenic acid (ALA), gamma-linolenic acid (GLA), linoleic acid (LA), arachidonic acid (AA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and docosapentaenoic acid (DPA). 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.

Based upon pooled data, patients on mipomersen have a higher risk for hepatic steatosis. Mipomersen is contraindicated in those with moderate or severe hepatic dysfunction or active liver disease, including unexplained persistent elevations of serum transaminases. It is also contraindicated in those that have a known sensitivity to product components.

Limitations of Use:
Juxtapid-

- 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) (1).

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

Kynamro-

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

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