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

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

This is a FlexRx Standard and GenRx Standard prior authorization program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
8/1/2023	4/1/2016

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Juxtapid® (lomitapide) Capsule	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		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Homozygous familial hypercholesterolemia (HoFH)	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 greater than 13 mmol/L (greater than 500 mg/dL), or a treated LDL-C concentration of greater than or equal to 8 mmol/L (greater than or equal to 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.(2,3) The American Heart Association released a scientific statement for familial hypercholesterolemia that recommended lomitapide may be considered in HoFH patients once a four-drug combination is needed (after rosuvastatin or atorvastatin +

<table>
<tr><td></td><td>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).(5)

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 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.(2)

The American Association of Clinical Endocrinologists (AACE) 2017 guidelines state that lomitapide may be useful for individuals with HoFH not responsive to PCSK9 therapy.(6)

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 and PCSK9 agents. Additional options include LDL apheresis or liver transplantation.(4)</td></tr>
<tr><td>Safety(1)</td><td>Lomitapide has a boxed warning for risk of hepatotoxicity. It 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.

Lomitapide is available only through a Risk Evaluation and Mitigation Strategy (REMS) program to ensure proper prescribing of the specific agent.

Contraindications for lomitapide:

• Pregnancy
• Concomitant use of moderate or strong CYP3A4 inhibitors

<table>
<tr><td>Moderate CYP3A4 inhibitors</td><td>Diltiazem

Fluconazole

Erythromycin</td></tr>
<tr><td>Strong CYP3A4</td><td>Itraconazole or ketoconazole

Erythromycin/clarithromycin

HIV protease inhibitors

nefazodone</td></tr>
</table>
</td></tr>
</table>

	• Moderate to severe hepatic impairment (based on Child-Pugh category B or C), or active liver disease including unexplained persistent abnormal liver function tests

REFERENCES

Number	Reference
1	Juxtapid prescribing information. Aegerion Pharmaceuticals, Inc. Cambridge, MA. September 2020.
2	Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *European Heart Journal*. 2014; 35(32):2146-2157. https://doi.org/10.1093/eurheartj/ehu274
3	National Collaborating Centre for Primary Care (UK). Identification and Management of Familial Hypercholesterolaemia (FH) [Internet]. London: Royal College of General Practitioners (UK); 2008 Aug. (NICE Clinical Guidelines, No. 71.) 3, Diagnosis. Available from: http://www.ncbi.nlm.nih.gov/books/NBK53822/
4	National Organization for Rare Disorders (NORD). Physician guide to Homozygous Familial Hypercholesterolemia (HoFH). https://rarediseases.org/physician-guide/homozygous-familial-hypercholesterolemia-hofh/
5	American Heart Association Scientific Statement: The Agenda for Familial Hypercholesterolemia. *Circulation* 2015; 132: 2167-2192.
6	Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular disease. AACE 2017 Guidelines. *Endocrine Practice*. 2017 Apr;23 (Suppl 2):1-87. doi: 10.4158/EP171764.APPGL. PMID: 28437620.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Juxtapid	lomitapide mesylate cap	10 MG ; 20 MG ; 30 MG ; 5 MG	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Juxtapid	lomitapide mesylate cap	10 MG ; 20 MG ; 30 MG ; 5 MG	30	Capsules	30	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Juxtapid	lomitapide mesylate cap	10 MG ; 20 MG ; 30 MG ; 5 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Juxtapid	lomitapide mesylate cap	10 MG ; 20 MG ; 30 MG ; 5 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** 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: 1. The patient has a diagnosis of homozygous familial hypercholesterolemia (HoFH) confirmed by ONE of the following: A. Genetic confirmation of two mutant alleles at the *LDLR, Apo-B, PCSK9, ARH* adaptor protein 1/*LDLRAP1* gene locus **OR** B. History of untreated LDL-C greater than 500 mg/dL (greater than 13 mmol/L) or treated LDL-C greater than or equal to 300 mg/dL (greater than or equal to 7.76 mmol/L) with ONE of the following:

Module	Clinical Criteria for Approval
	1. The patient had cutaneous or tendon xanthoma before age 10 years **OR** 2. Untreated elevated cholesterol levels consistent with heterozygous FH in both parents [untreated LDL-C greater than 190 mg/dL (greater than 4.9 mmol/L) or untreated total cholesterol greater than 290 mg/dL (greater than 7.5 mmol/L)] **AND** 2. ONE of the following: A. The patient is currently being treated with 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 an intolerance, or hypersensitivity to ALL of these therapies (i.e., rosuvastatin in combination with ezetimibe AND atorvastatin in combination with ezetimibe) **OR** C. The patient has an FDA labeled contraindication to ALL of these therapies (i.e., rosuvastatin in combination with ezetimibe AND atorvastatin in combination with ezetimibe) **OR** D. The patient is currently being treated with the requested agent as indicated by ALL of the following: 1. A statement by the prescriber that the patient is currently taking the requested agent **AND** 2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** 3. The prescriber states a change in therapy is expected to be ineffective or cause harm **OR** E. The prescriber has provided documentation that ALL therapies (i.e., rosuvastatin in combination with ezetimibe AND atorvastatin in combination with ezetimibe) 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 **AND** 3. ONE of the following: A. The patient has tried with adherence for at least 3 months and had an inadequate response to a PCSK9 inhibitor [e.g., Repatha (evolocumab), Praluent (alirocumab)] **OR** B. The patient has an intolerance or hypersensitivity to ALL PCSK9 inhibitors **OR** C. The patient has an FDA labeled contraindication to ALL PCSK9 inhibitors **OR** D. The patient is currently being treated with the requested agent as indicated by ALL of the following: 1. A statement by the prescriber that the patient is currently taking the requested agent **AND** 2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** 3. The prescriber states a change in therapy is expected to be ineffective or cause harm **OR** E. The prescriber has provided documentation that ALL PCSK9 inhibitors 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 **AND** 4. The patient is taking daily vitamin E, linoleic acid, alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) supplements **OR**

Module	Clinical Criteria for Approval
	B. The patient has another FDA approved indication for the requested agent and route of administration **OR** C. The patient has another indication that is supported in compendia for the requested agent and route of administration **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 the requested agent **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved for renewal when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. If the patient's diagnosis is homozygous familial hypercholesterolemia, BOTH of the following: A. ONE of the following: 1. The patient is currently being treated with 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 an intolerance or hypersensitivity to ALL of these therapies (i.e., rosuvastatin in combination with ezetimibe AND atorvastatin in combination with ezetimibe) **OR** 3. The patient has an FDA labeled contraindication to ALL of these therapies (i.e., rosuvastatin in combination with ezetimibe AND atorvastatin in combination with ezetimibe) **OR** 4. 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 a change in therapy is expected to be ineffective or cause harm **OR** 5. The prescriber has provided documentation that ALL therapies (i.e., rosuvastatin in combination with ezetimibe AND atorvastatin in combination with ezetimibe) 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 **AND** B. The patient is taking daily vitamin E, linoleic acid, alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) supplements **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. 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

Module	Clinical Criteria for Approval
	Length of Approval: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) is greater than the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. 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