Drug and Biologic Coverage Policy

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Coverage Policy Number 1507

Lomitapide Mesylate

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INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Lomitapide (Juxtapid®) is considered medically necessary when ALL of the following criteria are met:

- Documented diagnosis of homozygous familial hypercholesterolemia (HoFH) in an adult (18 years of age and older) as demonstrated by EITHER of the following:
  - Genetic confirmation of 2 mutant alleles at the LDL receptor, ApoB, PCSK9 or ARH adaptor protein gene locus OR
  - An untreated LDL-cholesterol concentration greater than 500 mg/dL OR a total treated LDL-C greater than or equal to 300 mg/dL AND one of the following:
    - The patient has clinical manifestations of HoFH (for example, cutaneous xanthomas before the age of 10 years, tendon xanthomas) OR
    - Untreated LDL cholesterol levels consistent with heterozygous familial hypercholesterolemia in both parents (greater than 190 mg/dL)

- Inadequate response (LDL-C greater than 70 mg/dL if ASCVD present OR LDL-C greater than 100 mg/dL if HoFH and no ASCVD) with maximally tolerated lipid lowering therapy regimen (high-intensity statin, ezetimibe, LDL apheresis where available) AND use will be adjunctive to diet and maximally tolerated lipid lowering therapy (unless contraindicated or intolerant).

- Inadequate response (i.e., LDL-C greater than 70 mg/dL if ASCVD present OR LDL-C greater than 100 mg/dL if HoFH and no ASCVD) after a minimum 3 month trial, contraindication per FDA label, documented intolerance, inability to use, or not a candidate for evolocumab (Repatha®)*
  * *Please note: May require prior authorization.*

- Lomitapide (Juxtapid®) will not be concomitantly administered with a PCSK9 monoclonal antibody (for example, Praluent®, Repatha®).

- Absence of moderate or severe hepatic impairment (based on Child-Pugh category B or C), active liver disease or unexplained persistent abnormal liver function tests

Initial authorization is up to 6 months

Lomitapide (Juxtapid®) is considered medically necessary for continued use when the initial criteria are met and BOTH of the following:
- Documented evidence of clinical beneficial response (for example, demonstrated reduction of LDL-C)
- Lomitapide (Juxtapid®) is used in combination with maximally tolerated lipid lowering therapy.

Reauthorization is for up to 12 months

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Lomitapide (Juxtapid®) is considered experimental, investigational or unproven for ANY other use including the following:
- Concurrent use of lomitapide (Juxtapid®) with alirocumab (Praluent®) or evolocumab (Repatha®)
- Heterozygous Familial Hypercholesterolemia (HeFH)
- Other forms of hyperlipidemia (for example, primary hyperlipidemia, mixed dyslipidemia)

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

FDA Approved Indications

FDA Approved Indication
Juxtapid is indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDLC), 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.

Recommended Dosing

FDA Recommended Dosing
***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

- Before treatment, measure ALT , AST, alkaline phosphatase, and total bilirubin; obtain a negative pregnancy test in females of reproductive potential; and initiate a low-fat diet supplying <20% of energy from fat.

- Initiate treatment at 5 mg once daily. Titrate dose based on acceptable safety/tolerability: increase to 10 mg daily after at least 2 weeks; and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and up to the maximum recommended dose of 60 mg daily.

- 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.

- Take once daily, whole, with water and without food, at least 2 hours after evening meal.

- Patients with end-stage renal disease on dialysis or with baseline mild hepatic impairment should not exceed 40 mg daily.

Drug Availability
Juxtapid is available in capsule form in 5 mg, 10 mg, 20 mg. 30 mg, 40 mg. and 60 mg.

Because of the risk of hepatotoxicity associated with Juxtapid therapy, Juxtapid is available through a restricted program under the REMS. Under the Juxtapid REMS, only certified healthcare providers and pharmacies may prescribe and distribute Juxtapid.

General Background

OVERVIEW
Juxtapid, a microsomal triglyceride transfer protein inhibitor, is indicated as an adjunct to a low fat diet and other lipid modifying therapies, including low-density lipoprotein (LDL) apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (total-C), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).[1] Limitations of use include that the safety and efficacy of Juxtapid have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH).[1] Also, the effect of Juxtapid on cardiovascular (CV) morbidity and mortality have not been determined. Repatha® (evolocumab injection for subcutaneous [SC] use), a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor, is indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional LDL-C lowering.[2] It is notable that patients known to have two LDL-receptor negative alleles (little or no residual function) did not respond to Repatha. Repatha is well-tolerated and is not associated with hepatotoxicity.[2] Simvastatin, atorvastatin, and rosuvastatin are statins that are indicated for the management of patients with HoFH.[3-5] Ezetimibe is also indicated for use in combination with atorvastatin or simvastatin in patients with HoFH.[6] Ezetimibe/simvastatin tablets are indicated for use in HoFH.[7]

Disease Overview
Familial hypercholesterolemias encompass a group of genetic defects that cause severe elevations in LDL-C levels, as well as other lipid parameters.[8] The condition occurs in approximately 1 in 300 to 500 patients and is present in childhood. There are approximately 1 in one million people with HoFH that have extreme hypercholesterolemia with rapidly advancing atherosclerosis if untreated. Currently known causes of familial hypercholesterolemia include mutations in low-density lipoprotein receptor (LDLR), apolipoprotein B (apo B), or proprotein convertase subtilisin kexin type 9 (PCSK9) genes. Over 1,600 known mutations of the LDLR gene have been documented to cause familial hypercholesterolemia and account for about 85% to 90% of familial hypercholesterolemia cases. Patients with familial hypercholesterolemia may have physical findings such as tendon xanthomas, which may occur at a young age. Individuals with familial hypercholesterolemia are at very high risk of coronary heart disease (CHD) at a premature age. Aggressive lipid modifying therapy is recommended to achieve LDL-C reductions of at least 50%. Both children and adults with LDL-C levels ≥ 190 mg/dL following lifestyle modifications will require medication therapy. Statins are the initial treatment for familial hypercholesterolemia. Higher risk patients may require intensification of drug therapy to achieve the more aggressive treatment goals. Intensification of medication therapy should be considered if LDL-C remains ≥ 160 mg/dL or if an initial 50% reduction in LDL-C is not achieved. Other non-statin therapies that can be considered include ezetimibe, Repatha, a bile acid sequestrant (colesevelam tablets or oral suspension), or niacin. Most

patients that cannot take a statin will require combination medication therapy. LDL apheresis is recommended in certain circumstances. Patients with HoFH should be managed by a lipid specialist.

Guidelines
In 2014, the European Atherosclerosis Society published recommendations regarding HoFH.[9] It notes that HoFH is a rare and life-threatening condition characterized by plasma cholesterol levels > 500 mg/dL, extensive xanthomas, and premature clinical atherosclerotic cardiovascular disease (ASCVD). If untreated, patients with extremely elevated LDL-C levels may develop atherosclerosis prior to the second decade of life. The frequency of HoFH is estimated at 1 in one million patients. The diagnosis of HoFH can be done by genetic or clinical criteria (see Table 1 below).

Table 1. Criteria for the Diagnosis of HoFH.[9]
• Genetic confirmation of two mutant alleles at the LDLR, Apo B, PCSK9 or LDLRAP1 gene locus; OR
• An untreated LDL-C > 500 mg/dL* or treated LDL-C > 300 mg/dL* together with either 1) cutaneous or tendon xanthoma before the age of 10 years or 2) untreated elevated LDL-C levels consistent with heterozygous FH in both parents.

HoFH – Homozygous familial hypercholesterolemia; LDLR – Low-density lipoprotein receptor; Apo B – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9; LDLRAP1 – Low-density lipoprotein receptor adaptor protein 1; LDL-C – Low-density lipoprotein cholesterol; * These cited LDL-C levels are only indicative and lower levels, especially in children or in untreated patients do not exclude HoFH; FH – Familial hypercholesterolemia.

The Consensus panel strongly recommends that lipid modifying therapy be initiated as early as possible based on evidence that treatment can delay the onset of clinically evident ASCVD.[9] LDL-C targets in HoFH are < 100 mg/dL in adults [< 135 mg/dL in children] or < 70 mg/dL in adults with clinical ASCVD. Statins have been the prominent treatment in HoFH, even among individuals who are receptor negative. Ezetimibe also provides further reduction. Combination therapy may also include other agents such as bile acid sequestrants, niacin and fibrates. LDL apheresis is also utilized and can decrease plasma LDL-C levels by 55% to 70% relative to pre-treatment levels. These guidelines were published before approval of Repatha which is indicated for use in HoFH.

In 2018, The American College of Cardiology/American Heart Association (ACC/AHA) released comprehensive guidelines addressing treatment of elevated cholesterol to reduce atherosclerotic cardiovascular risk. These guidelines only briefly mention familial hypercholesterolemia to address the importance of screening for familial hypercholesterolemia in patients with LDL-C $\geq$190 mg/dL, and to confirm that the primary goal in familial hypercholesterolemia is a 50% reduction in LDL-C. For HoFH, treatment options include statins, ezetimibe, lomitapide, PCSK9 inhibitors, and lipid apheresis. Lomitapide was not addressed specifically in these guidelines.[11]

The American College of Cardiology (ACC) released a 2017 focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk. ACC states lomitapide may be needed to control LDL-C in patients with ASCVD and baseline LDL-C >190 mg/dL and/or phenotypic HoFH who have an inadequate response to statins with or without ezetimibe and PCSK9 inhibitors.[12]

Safety
Juxtapid has a Boxed Warning regarding the risk of hepatotoxicity.[1] Juxtapid may cause elevations in liver transaminases. Also, Juxtapid increases hepatic fat (hepatic steatosis) with or without concomitant increases in transaminases. Due to the risk of hepatotoxicity, Juxtapid is available only through a Risk Mitigation and Strategy (REMS) Program. Juxtapid is a Pregnancy Category X medication and may cause fetal harm when given to a pregnant woman based on findings suggesting teratogenicity in animals. Females of reproductive potential should obtain a negative pregnancy test before Juxtapid initiation and should utilize effective contraception during Juxtapid use. Juxtapid is associated with gastrointestinal (GI) adverse events (AEs), which occurred in 93% of patients (n = 27/29). GI AEs included diarrhea (79%), nausea (65%), dyspepsia (38%), vomiting (34%), and abdominal pain (34%). Postmarketing reports regarding severe diarrhea have been associated with use of Juxtapid which have involved hospitalization of patients due to diarrhea-related complications such as volume depletion.

Experimental Investigational, Unproven Uses

- **The concurrent use of Juxtapid with alirocumab (Praluent) or evolocumab (Repatha)**. Repatha, specifically indicated in HoFH, and Praluent are PCSK9 inhibitors and have not been studied concomitantly with Juxtapid therapy.

- **The use of Juxtapid in patients with Heterozygous Familial Hypercholesterolemia (HeFH).** The safety and effectiveness of Juxtapid have not been established in patients with hypercholesterolemia who do not have HoFH, including those with HeFH.[1]

- **The use of Juxtapid in patients with other forms of hyperlipidemia (e.g., primary hyperlipidemia, mixed dyslipidemia).** The safety and efficacy of Juxtapid have not been established in patients with hypercholesterolemia who do not have HoFH.[1]

Coding/ Billing Information

Note: Lomitapide mesylate is typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.

References

1. Juxtapid® capsules [prescribing information]. Cambridge, MA: Aegerion Pharmaceuticals; December 2019.
2. Repatha® injection for subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen; February 2019.
3. Zocor® tablets [prescribing information]. Whitehouse Station, NJ: Merck; September 2020.
4. Lipitor® tablets [prescribing information]. New York, NY: Pfizer; September 2020.
5. Crestor® tablets [prescribing information]. Wilmington, DE: AstraZeneca; May 2020.
6. Zetia® tablets [prescribing information]. Whitehouse Station, NJ: Merck; August 2013.
7. Vytorin® tablets [prescribing information]. Whitehouse Station, NJ: Merck; September 2020.
8. Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients. J Clin Lipidol. 2011;5:S1-S8.
9. Cuchel M, Bruckert E, Ginsberg HN, et al, for the European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia. Homozygous familial hypercholesterolemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolemia of the European Atherosclerosis Society. Eur Heart J. 2014;35:2146-2157.
10. Raal FJ, Hovingh GK, Catapano AL. Familial hypercholesterolemia treatments: guidelines and new therapies. Atherosclerosis. 2018 Oct;277:483-492.
11. Grundy SM, Stone NJ, Bailey AL, et al ACC/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2018 Nov 10. [Epub ahead of print]. Available at: https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000625.
12. Lloyd-Jones DM, Morris PB, Ballantyne CM. 2017 focused update of the 2016 ACC Expert Consensus Decision Pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk. J Am Coll Cardiol. 2017;70(14):1785-1822.