Clinical Policy: Lomitapide (Juxtapid)

Reference Number: ERX.SPA.170
Effective Date: 01.11.17
Last Review Date: 02.22
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Lomitapide (Juxtapid®) is a microsomal triglyceride transfer protein inhibitor.

FDA Approved Indication(s)

Juxtapid is 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).

Limitation(s) 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.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Juxtapid is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Homozygous Familial Hypercholesterolemia (must meet all)**:**

1. Diagnosis of HoFH defined as one of the following (a, b, or c):
   a. Genetic mutation indicating HoFH (e.g., mutations in low density lipoprotein receptor [LDLR] gene, proprotein convertase subtilisin kexin 9 [PCSK9] gene, apo B gene, low density lipoprotein receptor adaptor protein 1 [LDLRAP1] gene);
   b. Treated LDL-C ≥ 300 mg/dL or non-HDL-C ≥ 330 mg/dL;
   c. Untreated LDL-C ≥ 500 mg/dL, and one of the following (i or ii):
      i. Tendinous or cutaneous xanthoma prior to age 10 years;
      ii. Evidence of HeFH in both parents (e.g., documented history of elevated LDL-C ≥ 190 mg/dL prior to lipid-lowering therapy);
2. Prescribed by or in consultation with a cardiologist, endocrinologist, or lipid specialist;
3. Age ≥ 18 years;
4. Documentation of recent (within the last 60 days) LDL-C ≥ 70 mg/dL;
5. For members on statin therapy, both of the following (a and b):
   a. Juxtapid is prescribed in conjunction with a statin at the maximally tolerated dose;
   b. Member has been adherent for at least the last 4 months to maximally tolerated doses of one of the following statin regimens (i, ii, or iii):
      i. A high intensity statin (*see Appendix D*);
      ii. A moderate intensity statin (*see Appendix D*), and member has one of the following (a or b):

a) Intolerance to two high intensity statins;
b) A statin risk factor (*see Appendix F*);

iii. A low intensity statin, and member has one of the following (a or b):
a) Intolerance to one high and one moderate intensity statins;
b) A statin risk factor (*see Appendix F*) and history of intolerance to two moderate intensity statins;

6. For members not on statin therapy, member meets one of the following (a or b):
   a. Statin therapy is contraindicated per Appendix E;
   b. For members who are statin intolerant, member has tried at least two statins, one of which must be hydrophilic (pravastatin, fluvastatin, or rosuvastatin), and member meets one of the following (i or ii):
      i. Member has documented statin risk factors (*see Appendix F*);
      ii. Member is statin intolerant due to statin-associated muscle symptoms (SAMS) and meets both of the following (a and b):
         a) Documentation of intolerable SAMS persisting at least two weeks, which disappeared with discontinuing the statin therapy and recurred with a statin re-challenge;
         b) Documentation of re-challenge with titration from lowest possible dose and/or intermittent dosing frequency (e.g., 1 to 3 times weekly);
7. Member has been adherent to ezetimibe therapy used concomitantly with a statin at the maximally tolerated dose for at least the last 4 months, unless contraindicated per Appendix E or member has a history of ezetimibe intolerance (e.g., associated diarrhea or upper respiratory tract infection);
8. Failure of Praluent®, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required for Praluent*
9. Treatment plan does not include coadministration with Repatha® or Praluent;
10. Dose does not exceed 60 mg (two capsules) per day.

Approval duration: 6 months

B. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Homozygous Familial Hypercholesterolemia (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. If statin tolerant, documentation of adherence to a statin at the maximally tolerated dose;
3. Member is responding positively to therapy as evidenced by lab results within the last 3 months showing an LDL-C reduction since initiation of Juxtapid therapy;
4. If request is for a dose increase, new does not exceed 60 mg (two capsules) per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALT: alanine aminotransferase
apoB: apolipoprotein B
FDA: Food and Drug Administration
HDL-C: high-density lipoprotein cholesterol
HeFH: heterozygous familial hypercholesterolemia
HoFH: homozygous familial hypercholesterolemia
LDL-C: low density lipoprotein cholesterol
LDLR: low density lipoprotein receptor
LDLRAP1: low density lipoprotein receptor adaptor protein 1
PCSK9: proprotein convertase subtilisin kexin 9
SAMS: statin-associated muscle symptoms
TC: total cholesterol
ULN: upper limit of normal

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
ezetimibe/simvastatin (Vytorin®)	10/40 mg PO QD	10 mg-40 mg/day (use of the 10/80 mg dose is restricted to patients who have been taking simvastatin 80 mg for ≥ 12 months without evidence of muscle toxicity)
ezetimibe (Zetia®)	10 mg PO QD	10 mg/day
atorvastatin (Lipitor®)	40 mg PO QD	80 mg/day
rosuvastatin (Crestor®)	5 - 40 mg PO QD	40 mg/day
Praluent® (alirocumab)	150 mg SC every 2 weeks	300 mg/month

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Pregnancy
  - Concomitant use with strong or moderate CYP3A4 inhibitors
  - Moderate or severe hepatic impairment (Child-Pugh B or C) or active liver disease, including unexplained persistent elevations of serum transaminases
- Boxed warning(s): risk of hepatotoxicity

Appendix D: High and Moderate Intensity Daily Statin Therapy for Adults

High Intensity Statin Therapy ***Daily dose shown to lower LDL-C, on average, by approximately ≥ 50%***
• Atorvastatin 40-80 mg • Rosuvastatin 20-40 mg
Moderate Intensity Statin Therapy ***Daily dose shown to lower LDL-C, on average, by approximately 30% to 50%***
• Atorvastatin 10-20 mg • Fluvastatin XL 80 mg • Fluvastatin 40 mg BID • Lovastatin 40 mg • Pitavastatin 1-4 mg • Pravastatin 40-80 mg • Rosuvastatin 5-10 mg • Simvastatin 20-40 mg
Low Intensity Statin Therapy ***Daily dose shown to lower LDL-C, on average, by < 30%***
• Simvastatin 10 mg

Low Intensity Statin Therapy ***Daily dose shown to lower LDL-C, on average, by < 30%***
• Pravastatin 10-20 mg • Lovastatin 20 mg • Fluvastatin 20-40 mg

Appendix E: Statin and Ezetimibe Contraindications

Statins
• Decompensated liver disease (development of jaundice, ascites, variceal bleeding, encephalopathy) • Laboratory-confirmed acute liver injury or rhabdomyolysis resulting from statin treatment • Pregnancy*, actively trying to become pregnant, or nursing • Immune-mediated hypersensitivity to the HMG-CoA reductase inhibitor drug class (statins) as evidenced by an allergic reaction occurring with at least TWO different statins
Ezetimibe
• Moderate or severe hepatic impairment [Child-Pugh classes B and C] • Hypersensitivity to ezetimibe (e.g., anaphylaxis, angioedema, rash, urticaria)

**In July 2021, the FDA requested removal of the contraindication against use of statins in pregnant women. Because the benefits of statins may include prevention of serious or potentially fatal events in a small group of very high-risk pregnant patients, contraindicating these drugs in all pregnant women is not appropriate.*
https://www.fda.gov/safety/medical-product-safety-information/statins-drug-safety-communication-fda-requests-removal-strongest-warning-against-using-cholesterol

Appendix F: Statin Risk Factors

Statin Risk Factors
• Multiple or serious comorbidities, including impaired renal or hepatic function • Unexplained alanine transaminase (ALT) elevations > 3 times upper limit of normal, or active liver disease • Concomitant use of drugs adversely affecting statin metabolism • Age > 75 years, or history of hemorrhagic stroke • Asian ancestry

Appendix G: General Information

- Because of the risk of hepatotoxicity, Juxtapid is available only through a Risk Evaluation and Mitigation Strategy (REMS) program called the Juxtapid REMS Program.
- Low density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene is also known as autosomal recessive hypercholesterolemia (ARH) adaptor protein 1 gene.
- The diagnosis of SAMS is often on the basis of clinical criteria. Typical SAMS include muscle pain and aching (myalgia), cramps, and weakness. Symptoms are usually bilateral and involve large muscle groups, including the thigh, buttock, back, and shoulder girdle musculature. In contrast, cramping is usually unilateral and may involve small muscles of the hands and feet. Symptoms may be more frequent in physically active patients. Symptoms often appear early after starting stain therapy or after an increase in dose and usually resolve or start to dissipate within weeks after cessation of therapy, although it may take several months for symptoms to totally resolve. Persistence of symptoms for more than 2 months after drug cessation should prompt a search for other causes or for underlying muscle disease possibly provoked by statin therapy. The reappearance of symptoms with statin rechallenge and their disappearance with drug cessation offers the best evidence that the symptoms are truly SAMS.
- Pravastatin, fluvastatin, and rosuvastatin are hydrophilic statins which have been reported to confer fewer adverse drug reactions than lipophilic statins.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
HoFH	5 mg PO QD up to maximum dose following a specific titration schedule as follows (dose: duration of administration before considering increase to next dosage): • 5 mg QD: At least 2 weeks • 10 mg QD: At least 4 weeks • 20 mg QD: At least 4 weeks • 40 mg QD: At least 4 weeks • 60 mg QD: Max recommended dosage Doses should be escalated gradually based on acceptable safety and tolerability. Transaminases should be measured prior to any increase in dose Modify dosing for patients taking concomitant cytochrome P450 (CYP) 3A4 inhibitors, renal impairment, or baseline hepatic impairment. Dose adjustments are also required for patients who develop transaminase values at least 3x ULN during Juxtapid treatment.	60 mg/day

VI. Product Availability

Capsules: 5 mg, 10 mg, 20 mg, 30 mg

VII. References

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2018 annual review: added age limit; lowered minimum LDL value required for initial approval from 100 mg/dL to 70 mg/dL; revised trial of ezetimibe language by requiring concomitant statin; added treatment plan does not include Kynamro, Repatha, or Praluent; revised positive response to therapy as a general LDL reduction from specific cut-off values; references reviewed and updated.	05.22.18	08.18
1Q 2019 annual review: no significant changes; references reviewed and updated.	11.20.18	02.19
1Q 2020 annual review: increased the timeframe for LDL-C lab draws from 30 days to 60 days; concomitant statin usage section modified to more clearly delineate between patients who are currently on statin therapy vs. those who are not, and for the latter, to require documentation of a prior trial of two statins with documentation of statin risk factors or intolerance; criteria for statin-rechallenge in the setting of SAMS are added; Appendix D updated based on 2018 ACC/AHA guidelines; added Medicaid line of business with 3 month initial approval duration; references reviewed and updated.	11.05.19	02.20
1Q 2021 annual review: added requirement for adherence to statin therapy on re-auth; modified initial approval duration for Medicaid from 3 to 6 months; references reviewed and updated.	11.02.20	02.21
1Q 2022 annual review: no significant changes; modified redirection from Repatha to Praluent based on formulary status; removed references to Kynamro since it has been withdrawn from market; removed 40 mg and 60 mg capsules per updated PI; references reviewed and updated.	10.01.21	02.22

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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