RXADVANCE
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Clinical Policy Title:	lomitapide
Policy Number:	RxA.604
Drug(s) Applied:	Juxtapid®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

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

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
lomitapide (Juxtapid®)	HoFH	5 mg PO once daily up to maximum dose following a specific titration schedule as follows: [Dosage – duration of administration before considering increase to next dosage] 5 mg once daily – at least 2 weeks 10 mg, 20mg, 40 mg once daily – at least 4 weeks for each dose • Doses should be escalated gradually based on acceptable safety and tolerability. • 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

Dosage Forms

- Capsules: 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 60 mg.

Clinical Policy

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

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 G);
      ii. A moderate intensity statin (see Appendix G) 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, 1 of which must be hydrophilic statins (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 Repatha®, unless contraindicated or clinically significant adverse effects are experienced; **Prior authorization may be required for Repatha.*
9. Treatment plan does not include coadministration with Kynamro®, Repatha®, or Praluent®;
10. Dose not exceed 60 mg per day.

Approval duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Homozygous Familial Hypercholesterolemia (must meet all):

1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy
2. 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;
3. If request is for a dose increase, new dose does not exceed 60 mg (one capsule) per day.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

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
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PCSK9: proprotein convertase subtilisin kexin 9
TC: total cholesterol
ULN: upper limit of normal

APPENDIX B: Therapeutic Alternatives

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Maximum Dose
ezetimibe/ simvastatin (Vytorin®)	10/40 mg PO once daily	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 or more without evidence of muscle toxicity)

Drug Name	Dosing Regimen	Maximum Dose
ezetimibe (Zetia®)	10 mg PO once daily	10 mg/day
atorvastatin (Lipitor®)	40 mg PO once daily	80 mg/day
rosuvastatin (Crestor®)	5 - 40 mg PO once daily	40 mg/day
Repatha® (evolocumab)	420 mg SC once monthly	420 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):
  - Moderate or severe hepatic impairment (Child-Pugh B or C)
  - Active liver disease, including unexplained persistent elevations of serum transaminases

- Boxed Warning(s):
  - Risk of hepatotoxicity

APPENDIX D: General Information

- The safety and effectiveness of Juxtapid® have not been established in pediatric patients.
- There is a black box warning on the package labeling for Juxtapid® regarding the risk of hepatotoxicity. In the Juxtapid® clinical trial 10 (34%) of the 29 patients treated with Juxtapid® had at least one elevation in alanine transaminase (ALT) or aspartate aminotransferase (AST) that was at least three times the upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, INR, or alkaline phosphatase. Juxtapid® also increases hepatic fat, with or without concomitant increases in transaminases. Hepatic steatosis associated with Juxtapid® treatment may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis. The package labeling for Juxtapid® recommends that ALT, AST, alkaline phosphatase, and total bilirubin be measured before treatment, and then ALT and AST regularly as recommended. During treatment, dose adjustments may be needed if ALT or AST are at least 3x ULN. Juxtapid® should be discontinued for clinically significant liver toxicity.
- Because of the risk of hepatotoxicity, Juxtapid® is available only through a Risk Evaluation and Mitigation Strategy (REMS) program called the Juxtapid® REMS Program.
- Juxtapid® has not been studied concomitantly with other LDL-lowering agents that can also increase hepatic fat. Therefore, the combined use of such agents is not recommended.
- Juxtapid® may cause fetal harm when administered to a pregnant woman. Females of reproductive potential should have a negative pregnancy test before starting Juxtapid® and should use effective contraception during therapy with Juxtapid®.
- Concomitant administration with moderate or strong CYP3A4 inhibitors can increase Juxtapid® exposure.
- Weak CYP3A4 inhibitors increase lomitapide exposure approximately 2-fold. Lomitapide dosage should not exceed 30 mg daily when it is used concomitantly with weak CYP3A4 inhibitors (such as alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, lapatinib, nilotinib, oral contraceptives, pazopanib, ranitidine, ranolazine, ticagrelor, zileuton).
- Low density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene is also known as autosomal

recessive hypercholesterolemia (ARH) adaptor protein 1 gene.

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)

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: 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 10-20mg • Fluvastatin XL 80 mg • Fluvastatin 40 mg 2x/day • Lovastatin 40 mg • Pitavastatin 2-4 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 • Pravastatin 10–20 mg • Lovastatin 20 mg • Fluvastatin 20–40 mg • Pitavastatin 1 mg

References

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Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	03/2019	03/06/2020
Policy was reviewed: 1. Policy title table was updated: Line of business policy applies was updated to All lines of business. 2. Appendix B language was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance…..". 3. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by	10/30/2020	12/07/2020

RxAdvance…”. 4. References were updated.		