Clinical Policy: Lomitapide (Juxtapid)

Reference Number: CP.PHAR.283
Effective Date: 10.01.16
Last Review Date: 02.19 Revision Log
Line of Business: Commercial, Medicaid

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.

It is the policy of health plans affiliated with Centene Corporation® 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 30 days) LDL-C ≥ 70 mg/dL;
5. Member has been adherent to a high intensity statin (*see Appendix D*) regimen for at least the last 4 months, unless one of the following applies (a, b, or c):
   a. Statin therapy is contraindicated per Appendix E;
   b. Member has been adherent to a moderate intensity statin (*see Appendix D*) regimen for at least the last 4 months due to one of the following (i or ii):
      i. Intolerance to two high intensity statins;
      ii. A statin risk factor (*see Appendix F*);
   c. Member is unable to take a high or moderate intensity statin due to one of the following (i or ii):
      i. Intolerance to two high and two moderate intensity statins;
      ii. A statin risk factor (*see Appendix F*) and history of intolerance to two moderate intensity statins;
6. 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);
7. Failure of Repatha®, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for Repatha*
8. Treatment plan does not include coadministration with Kynamro®, Repatha®, or Praluent®;
9. Dose not exceed 60 mg per day.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
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 per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial and CP.PMN.53 for Medicaid 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
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 for all relevant lines of business 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 or more 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
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: 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

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

Statin Risk Factors
• Age > 75 years, or history of hemorrhagic stroke • Asian ancestry

Appendix G: 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.

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: Dosage – duration of administration before considering increase to next dosage:	60 mg/day

Indication	Dosing Regimen	Maximum Dose
	5 mg QD – at least 2 weeks 10 mg, 20mg, 40 mg QD – 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.	

VI. Product Availability

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

VII. References

1. Juxtapid Prescribing Information. Cambridge, MA: Aegerion Pharmaceuticals, Inc.; August 2017. Available at: http://www.juxtapidpro.com/prescribing-information. Accessed May 22, 2018.
2. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 June 24; 129[suppl 2]: S1-S45.
3. Jacobson TA, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 – full report. Journal of Clinical Lipidology. March-April 2015; 9(2): 129-169. http://dx.doi.org/10.1016/j.jacl.2015.02.003
4. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. Journal of Clinical Lipidology. June 2011; 5(3S): 1-15
5. Fitchett DH, Hegele RA, Verma S. Statin intolerance. Circulation 2015;131:e389-391. https://doi.org/10.1161/CIRCULATIONAHA.114.013189.
6. Lloyd-Jones DM, Morris PB, Minissian MB, et al. 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. http://dx.doi.org/10.1016/j.jacc.2017.07.745

Reviews, Revisions, and Approvals	Date	P&T Approval Date
New policy – split from CP.PHAR.110 Juxtapid and Kynamro, and converted to new template. Removed age criteria. Changed signs from ">" to "≥" for following criteria per NLA FH guidelines: Treated LDL-C ≥ 300 mg/dL or non-HDL-C ≥ 330 mg/dL; Untreated LDL-C ≥ 500 mg/dL, and one of the following (i or ii): Evidence of HeFH in both parents (e.g., documented history of elevated LDL-C ≥ 190 mg/dL prior to lipid-lowering therapy). Added examples of Zetia intolerance. Incorporated HOFH, TLC appendices into the criteria. Combined Zetia and statin contraindications (App D) and added nursing as a contraindication. Statin risk factors are listed at App E. Added requirement for the use of statin and zetia therapy for the last 4 months. Modified approval duration to 6 months initial/12 month renewal.	10.16	10.16
Converted to new template. Safety criteria was applied according to the safety guidance discussed at CPAC and endorsed by Centene Medical Affairs.	09.17	10.17
3Q 2018 annual review: combined policies for Medicaid and Commercial lines of business; added age limit; Medicaid: removed requirement for therapeutic life style changes and counseling due to inability to objectively verify; removed contraindications from initial criteria; aligned trial of ezetimibe language with commercial by requiring concomitant statin; Commercial: added specific criteria from "member must meet criteria for Repatha"; reduced approval durations from LOB to 6 and 12 months; 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

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.