

Clinical Policy: Mipomersen (Kynamro)

Reference Number: CP.PHAR.284

Effective Date: 10.16

Last Review Date: 02.20

Line of Business: Commercial, Medicaid

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

Mipomersen (Kynamro[®]) is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis.

FDA Approved Indication(s)

Kynamro is indicated as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol (TC), 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 Kynamro have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH).
- The effect of Kynamro on cardiovascular morbidity and mortality has not been determined.
- The use of Kynamro as an adjunct to LDL apheresis is not recommended.

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 Kynamro 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 \geq 300 mg/dL or non-HDL-C \geq 330 mg/dL;
 - c. Untreated LDL-C \geq 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 \geq 190 mg/dL prior to lipid-lowering therapy);
2. Prescribed by or in consultation with a cardiologist, endocrinologist or lipid specialist;
3. Age \geq 18 years;

4. Documentation of recent (within the last 60 days) LDL-C \geq 70 mg/dL;
5. For members on statin therapy, both of the following (a and b):
 - a. Kynamro 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, 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 Juxtapid[®], Praluent[®], Repatha;
10. Dose does not exceed 200 mg per week.

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 Kynamro therapy;
3. If request is for a dose increase, new dose does not exceed 200 mg per week.

Approval duration: 12 months

B. Other diagnoses/indications (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 transaminase	LDL-C: low density lipoprotein cholesterol
apo B: apolipoprotein B	LDLR: low density lipoprotein receptor
FDA: Food and Drug Administration	LDLRAP1: low density lipoprotein receptor adaptor protein 1
HDL-C: high-density lipoprotein cholesterol	PCSK9: proprotein convertase subtilisin kexin 9
HeFH: heterozygous familial hypercholesterolemia	SAMS: statin-associated muscle symptoms
HoFH: homozygous familial hypercholesterolemia	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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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
<i>Daily dose shown to lower LDL-C, on average, by approximately ≥50%</i>
<ul style="list-style-type: none"> • Atorvastatin 40-80 mg • Rosuvastatin 20-40 mg
Moderate Intensity Statin Therapy
<i>Daily dose shown to lower LDL-C, on average, by approximately 30% to 50%</i>
<ul style="list-style-type: none"> • Atorvastatin 10-20mg • 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
<i>Daily dose shown to lower LDL-C, on average, by <30%</i>
<ul style="list-style-type: none"> • Simvastatin 10 mg • Pravastatin 10–20 mg • Lovastatin 20 mg • Fluvastatin 20–40 mg

Appendix E: Statin and Ezetimibe Contraindications

Statins
<ul style="list-style-type: none"> • 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

Statins
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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, Kynamro is available only through a Risk Evaluation and Mitigation Strategy (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 statin 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	200 mg SC once per week	200 mg/week

VI. Product Availability

Pre-filled syringe: 200 mg/mL

VII. References

1. Kynamro Prescribing Information. Chicago, IL: Kastle Therapeutics; May 2016. Available at: <http://www.kynamro.com>. Accessed October 29, 2019.
2. Grundy SM, Stone NJ, Bailey AL, et al. 2018 ACC/AHA/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 Foundation/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;Nov 10:[Epub ahead of print].
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. Goldber AC, Hopkins PN, Toth PP, et al. 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>.
7. Manpuya WM, Cho L, Frid D, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. *American Heart Journal* 2013; 166(3):597-603.
8. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings. *Ann of Intern Med* 2013; 158(7):526-534.
9. Backes JM, Ruisinger JF, Gibson CA, et al. Statin-associated muscle symptoms—managing the highly intolerant. *J Clin Lipidol*. 2017;11:24-33. Available at: <https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2017/05/03/10/43/statin-associated-muscle-symptoms>. Accessed June 10, 2019.
10. Thompson PD, Panza G, Zaleski A, et al. Statin-associated side effects. *JACC* 2016;67(20):2395-2410.

Reviews, Revisions, and Approvals	Date	Approval Date
<p>New policy – split from CP.PHAR.110 Juxtapid and Kynamro, and converted to new template. Removed age. 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).</p> <p>Added examples of Zetia intolerance. Added the following limitation per PI: member does not have severe renal impairment or clinically significant proteinuria, and is not on renal dialysis. Incorporated HOFH, TLC appendices into the criteria. Combined Zetia and statin contraindications (App C) 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.</p>	10.16	10.16
<p>Policy converted to new template. Safety criteria was applied according to the safety guidance discussed at CPAC and endorsed by Centene Medical Affairs.</p>	09.17	10.17
<p>3Q 2018 annual review: combined policies for Medicaid and Commercial lines of business; no significant changes from previously approved corporate policy; added age limit; Medicaid: removed requirement for therapeutic life style changes and counseling due to inability to objectively verify; removed requirement against concomitant administration of apheresis; removed requirement against use if renally impaired; aligned trial of Zetia language with commercial by requiring concomitant statin; Commercial: reduced approval durations from LOB to 6 and 12 months; references reviewed and updated.</p>	05.22.18	08.18
<p>1Q 2019 annual review: no significant changes; references reviewed and updated.</p>	11.20.18	02.19
<p>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; references reviewed and updated.</p>	11.05.19	02.20

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.

©2016 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.