Clinical Policy: Mipomersen (Kynamro)

Reference Number: PA.CP.PHAR.284
Effective Date: 01/18
Last Review Date: 01/19 Revision Log

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 (which may include office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of Pennsylvania Health and Wellness® 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 ≥ 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 ≥ 70mg/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);
   Failure of Repatha®, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for Repatha*
7. Treatment plan does not include coadministration with Juxtapid®, Praluent®, Repatha;
8. Dose does not exceed 200 mg per week.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to PA.CP.PMN.53 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 Pennsylvania Health and Wellness benefit or member has previously met initial approval criteria or Continuity of Care policy applies;
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 (must meet all)**:**

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met initial approval criteria; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy;

Approval duration: Duration of request or 6 months (whichever is less); or

3. Refer to PA.CP.PMN.53 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 – PA.CP.PMN.53 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALT: Alanine transaminase
apo B: 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 • Age > 75 years, or history of hemorrhagic stroke • Asian ancestry

Appendix G: General Information

- The safety and effectiveness of Kynamro have not been established in pediatric patients.
- The effect of Kynamro on cardiovascular morbidity and mortality has not been determined.
- The safety and effectiveness of Kynamro have not been established in pediatric patients.
- There is a black box warning on the package labeling for Kynamro regarding the risk of hepatotoxicity. In the Kynamro HoFH clinical trial 4 (12%) of the 34 patients treated with Kynamro compared to 0% of the 17 placebo-treated patients had an elevation in alanine transaminase (ALT) at least 3x upper limit of normal (ULN); and, 3 (9%) of those treated with Kynamro compared to 0% treated with placebo had at least one elevation in ALT of at least 5x ULN. Because of the risk of hepatotoxicity, Kynamro is available only through a Risk Evaluation and Mitigation Strategy (REMS) program.
- 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.

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: 1 mL of 200 mg/mL solution

VII. References

1. Kynamro Prescribing Information. Chicago, IL: Kastle Therapeutics; May 2016. Available at: http://www.kynamro.com. Accessed November 20, 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	Approval Date
Removed requirement for therapeutic life style changes and counseling due to inability to objectively verify; removed requirement against concomitant administration of aphresis; removed requirement against use if renally impaired; aligned trial of Zetia language with commercial by requiring concomitant statin; references reviewed and updated.	05.18	
1Q 2019 annual review: references reviewed and updated.	01.19	