Clinical Policy: Mipomersen (Kynamro)
Reference Number: CP.PHAR.284
Effective Date: 10.01.16
Last Review Date: 02.21
Line of Business: Commercial, Medicaid

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
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 ≥ 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. 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, 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 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®, or 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. 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 Kynamro therapy;
   4. 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
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
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 for all relevant lines of business and may require prior authorization.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ezetimibe/simvastatin</td>
<td>10/40 mg PO QD</td>
<td>10 mg-40 mg/day (use of the 10/80 mg dose is restricted to patients who have been taking</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Dosing Regimen</td>
<td>Dose Limit/Maximum Dose</td>
</tr>
<tr>
<td>---------------------------</td>
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<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>ezetimibe (Zetia®)</td>
<td>10 mg PO QD</td>
<td>10 mg/day</td>
</tr>
<tr>
<td>atorvastatin (Lipitor®)</td>
<td>40 mg PO QD</td>
<td>80 mg/day</td>
</tr>
<tr>
<td>rosuvastatin (Crestor®)</td>
<td>5 - 40 mg PO QD</td>
<td>40 mg/day</td>
</tr>
<tr>
<td>Repatha® (evolocumab)</td>
<td>420 mg SC once monthly</td>
<td>420 mg/month</td>
</tr>
</tbody>
</table>

*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) or active liver disease, including unexplained persistent elevations of serum transaminases
  - Known sensitivity to product components
- 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
- Pravastatin 10–20 mg
- Lovastatin 20 mg
- Fluvastatin 20–40 mg
Appendix E: Statin and Ezetimibe Contraindications

<table>
<thead>
<tr>
<th>Statin Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple or serious comorbidities, including impaired renal or hepatic function</td>
</tr>
<tr>
<td>Unexplained alanine transaminase (ALT) elevations &gt; 3 times upper limit of normal, or active liver disease</td>
</tr>
<tr>
<td>Concomitant use of drugs adversely affecting statin metabolism</td>
</tr>
<tr>
<td>Age &gt; 75 years, or history of hemorrhagic stroke</td>
</tr>
<tr>
<td>Asian ancestry</td>
</tr>
</tbody>
</table>

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 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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>HoFH</td>
<td>200 mg SC once per week</td>
<td>200 mg/week</td>
</tr>
</tbody>
</table>

VI. Product Availability

Single-use pre-filled syringe: 200 mg/mL

VII. References


Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.
CLINICAL POLICY
Mipomersen

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C9399</td>
<td>Unclassified drugs or biologicals</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy converted to new template. Safety criteria was applied according to the safety guidance discussed at CPAC and endorsed by Centene Medical Affairs.</td>
<td>09.17</td>
<td>10.17</td>
</tr>
<tr>
<td>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 aphresis; 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</td>
<td>05.22.18</td>
<td>08.18</td>
</tr>
<tr>
<td>1Q 2019 annual review: no significant changes; references reviewed and updated.</td>
<td>11.20.18</td>
<td>02.19</td>
</tr>
<tr>
<td>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.</td>
<td>11.05.19</td>
<td>02.20</td>
</tr>
<tr>
<td>1Q 2021 annual review: added requirement for adherence to statin therapy on re-auth; added coding implications; references reviewed and updated.</td>
<td>11.02.20</td>
<td>02.21</td>
</tr>
</tbody>
</table>

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
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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.

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**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.

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