Clinical Policy: Mipomersen (Kynamro)
Reference Number: ERX.SPMN.186
Effective Date: 01/2017
Last Review Date: 

See Important Reminder at the end of this policy for important regulatory and legal information.

Policy/Criteria
It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that mipomersen sodium injection (Kynamro®) is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Homozygous Familial Hypercholesterolemia (must meet all):
      1. Prescribed by or in consultation with a cardiologist, endocrinologist, or lipid specialist;
      2. Diagnosis of homozygous familial hypercholesterolemia (HoFH) defined as one of the following (a, b, or c):
         a. Genetic mutation indicating HoFH (LDLR, PCSK9, apoB, LDLRAP1);
         b. Treated low density lipoprotein cholesterol (LDL-C) ≥ 300 mg/dL or non-high density lipoprotein cholesterol (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 heterozygous familial hypercholesterolemia (HeFH) in both parents (e.g., documented history of elevated LDL-C ≥ 190 mg/dL prior to lipid-lowering therapy);
      3. Member meets one of the following (a or b):
         a. Age < 18 years and LDL-C ≥ 130 mg/dL within the last 30 days despite statin and Zetia therapy unless a contraindication (Appendix D) or history of intolerance to each such therapy;
         b. Age ≥ 18 years and recent (within the last 30 days) low-density lipoprotein cholesterol (LDL-C) ≥ 70 mg/dL;
      4. If member is ≥ 18 years, has received a high intensity statin (Appendix C) adherently for at least the last 4 months, unless one of the following applies (a, b, or c):
         a. Statin therapy is contraindicated per Appendix D;
         b. Member has received a moderate intensity statin (Appendix C) adherently for at least the last 4 months due to (i or ii):
            i. Intolerance to two high intensity statins;
            ii. A statin risk factor (Appendix E);
         c. Member is unable to take a high or moderate intensity statin due to (i or ii):
            i. Intolerance to two high and two moderate intensity statins;
            ii. A statin risk factor (Appendix E) and history of intolerance to two moderate intensity statins;
      5. If member is ≥ 18 years, has received Zetia therapy adherently for at least the last 4 months, unless contraindicated per Appendix D or a history of Zetia intolerance (e.g., associated diarrhea or upper respiratory tract infection);
6. Member has received counseling on therapeutic lifestyle changes (i.e., heart healthy diet; regular exercise; avoidance of tobacco products; maintenance of a healthy weight);
7. Failure of Repatha (evolocumab), unless contraindicated or intolerant;
8. Treatment plan does not include coadministration with Juxtapid (lomitapide), Repatha (evolocumab), Praluent (alirocumab), or LDL-C apheresis;
9. Prescribed dose of Kynamro does not exceed 200 mg once weekly.

Approval duration: 6 months

B. Other diagnoses/indications: Refer to ERX.SPMN.16 - Global Biopharm Policy.

II. Continued Approval
A. Homozygous Familial Hypercholesterolemia (must meet all):
   1. Currently receiving medication via health plan benefit or member has previously met all initial approval criteria;
   2. If member has been taking Kynamro for at least 6 months, lab results within the last 3 months are submitted showing an LDL-C reduction since initiation of Kynamro therapy;
   3. Prescribed dose of Kynamro does not exceed 200 mg once weekly.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2):
   1. Currently receiving medication via health plan benefit and documentation supports positive response to therapy; or
   2. Refer to ERX.SPMN.16 - Global Biopharm Policy.

Background
Description/Mechanism of Action:
Kynamro (mipomersen sodium) is a sterile, preservative-free, aqueous solution for subcutaneous injection. Mipomersen is an antisense oligonucleotide targeted to human messenger ribonucleic acid (mRNA) for apolipoprotein B-100 (apo B-100), the principal apolipoprotein of LDL and its metabolic precursor, very low-density lipoprotein cholesterol. Mipomersen is complementary to the coding region of the mRNA for apo B-100, and binds by Watson and Crick base pairing. The hybridization of mipomersen to the cognate mRNA results in RNase H-mediated degradation of the cognate mRNA thus inhibiting translation of the apo B-100 protein. The in vitro pharmacologic activity of mipomersen was characterized in human hepatoma cell lines (HepG2, Hep3B) and in human and cynomolgus monkey primary hepatocytes. In these experiments, mipomersen selectively reduced apo B mRNA, protein and secreted protein in a concentration- and time-dependent manner. The effects of mipomersen were shown to be highly sequence-specific. The binding site for mipomersen lies within the coding region of the apo B mRNA at the position 3249-3268 relative to the published sequence GenBank accession number NM_000384.1.
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**Mipomersen**

*Formulations:*
Kynamro: Single-use, 1 mL, clear glass pre-filled syringes filled to deliver 1 mL of solution containing 200 mg of mipomersen sodium (200 mg per 1 mL). Kynamro is available in cartons containing 1 or 4 pre-filled syringes.

*FDA Approved Indications:*
Kynamro is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis/subcutaneous injectable formulation indicated as:
- An adjunct to lipid-lowering medications and diet to reduce LDL-C, apo B, total cholesterol, and non-HDL-C in patients with HoFH.

Limitations of use:
- The safety and effectiveness of Kynamro have not been established in patients with hypercholesterolemia who do not have HoFH, including those with HeFH.
- The effect of Kynamro on cardiovascular morbidity and mortality has not been determined.
- The safety and effectiveness of Kynamro as an adjunct to LDL apheresis have not been established; therefore, the use of Kynamro as an adjunct to LDL apheresis is not recommended.

*Safety Information:*
Due to the risk of hepatotoxicity, Kynamro is available only through a restricted program called the Kynamro Risk Evaluation and Mitigation Strategy (REMS) program.

**Appendices**

**Appendix A: Abbreviation Key**
- apoB: apolipoprotein B
- ASCVD: atherosclerotic cardiovascular disease
- CVD: cardiovascular disease
- FH: familial hypercholesterolemia
- HDL-C: high-density lipoprotein cholesterol
- HeFH: heterozygous familial
- 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

**Appendix B: 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%*
o Simvastatin 10 mg  o Fluvastatin 20–40 mg
o Pravastatin 10–20 mg  o Pitavastatin 1 mg
o Lovastatin 20 mg

Appendix C: Statin and Zetia 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;

- Zetia
  - Moderate or severe hepatic impairment [Child-Pugh classes B and C];
  - Hypersensitivity to Zetia (e.g., anaphylaxis, angioedema, rash, urticaria).

Appendix D: Statin Risk Factors

- Multiple or serious comorbidities, including impaired renal or hepatic function;
- Unexplained ALT elevations > 3 times ULN, or active liver disease;
- Concomitant use of drugs adversely affecting statin metabolism;
- Age > 75 years, or history of hemorrhagic stroke;
- Asian ancestry.

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<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
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<tbody>
<tr>
<td>Policy split from USS.SPMN.32 Juxtapid and Kynamro, and converted to new template. Removed age. Changed signs from “&gt;” 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):</td>
<td>11/16</td>
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<td>- Tendinous or cutaneous xanthoma prior to age 10 years;</td>
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<td>- 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 and 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 D. 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.</td>
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**Clinical Policy**

Mipomersen

**References**


**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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.

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