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Medication Policy Manual | **Policy No:** dru301

Topic: Kynamro®, mipomersen | **Date of Origin:** May 16, 2013

Committee Approval Date: June 9, 2017 | **Next Review Date:** April 2018

Effective Date: July 1, 2017

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Mipomersen (Kynamro) is a self-administered injectable medication used in the treatment of homozygous familial hypercholesterolemia. It is an oligonucleotide inhibitor of apolipoprotein B-100, a necessary component in the formation of LDL.

Policy/Criteria

I. Most contracts require prior authorization approval of mipomersen (Kynamro) prior to coverage. Mipomersen (Kynamro) may be considered medically necessary in patients when criteria A and B below are met.

A. Documentation of a diagnosis of homozygous familial hypercholesterolemia established by or in conjunction with a specialist in cardiology or lipid management and there is clinical documentation of at least one of the following:

1. Genetic confirmation of two mutant alleles at the *LDLR, APOB, PCSK9,* or *LDLRAP1* gene locus

OR

2. An untreated low-density lipoprotein cholesterol (LDL-C) of > 500 mg/dL (or a treated LDL-C of > 300 mg/dL) with either:

   a. Cutaneous or tendon xanthoma before age 10 years

   OR

   b. Evidence of heterozygous familial hypercholesterolemia in both parents.

AND

B. Treatment with evolocumab (Repatha) was ineffective, not tolerated, or contraindicated.

II. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers mipomersen (Kynamro) to be a self-administered medication.

B. When prior authorization is approved, mipomersen (Kynamro) may be authorized in quantities of four 200mg/1 mL pre-filled syringes per month.

C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Mipomersen (Kynamro) is considered investigational when used for all other conditions, including, but not limited to:

A. Heterozygous familial hypercholesterolemia

B. Non-familial hyperlipidemia/hypercholesterolemia

C. In combination with lomitapide (Juxtapid®) or evolocumab (Repatha)

Position Statement

Summary

- Mipomersen (Kynamro) is used for the treatment of homozygous familial hypercholesterolemia (HoFH), a rare genetic disease characterized by abnormally elevated low-density lipoprotein cholesterol (LDL-C) levels.
- A diagnosis of HoFH is established through genetic testing or clinically by evaluating LDL-C levels, family history, and the presence of xanthomas.
- Because mipomersen (Kynamro) is linked to uncommon but serious side effects, it should be reserved for conditions where potential benefit outweighs risk, such as HoFH.
- Among the non-statins for HoFH, evolocumab (Repatha) is the best value for members.
- The safety and effectiveness of mipomersen (Kynamro) in conditions other than HoFH have not been established.

Background

- HoFH is a rare, genetic disease characterized by abnormally elevated LDL-C levels and an increased risk for early onset coronary heart disease. LDL-C levels can range from 300 to over 1000 mg/dL. If not treated, affected patients often die in early adulthood. [1]
- Treatment options include evolocumab (Repatha), lomitapide (Juxtapid), mipomersen (Kynamro), traditional lipid-lowering medications, and LDL-apheresis.[1,2]
- Treatment guidelines for HoFH recommend lifestyle modification and treatment with high doses statins (with or without ezetimibe), and LDL-apheresis. Mipomersen (Kynamro) should be considered as an adjunctive agent.[1,2]
- A diagnosis of HoFH is required as part of the FDA's Risk Evaluation and Mitigation Strategy (REMS) for both lomitapide (Juxtapid) and mipomersen (Kynamro). [3,4]
- The FDA approved prescribing information for mipomersen (Kynamro) states that it should not be used in patients with hypercholesterolemia who do not have HoFH, as safety and effectiveness have not been established in other settings.

Clinical Efficacy

HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Mipomersen (Kynamro) demonstrated LDL-C reduction is patients with HoFH; however, there is currently no evidence that it improves clinically meaningful outcomes, such as cardiovascular morbidity and mortality.

- A single randomized, placebo-controlled trial evaluated mipomersen (Kynamro) in 51 patients with HoFH. [5]
    - ***** Patients were also on maximally tolerated background therapy, including other lipid-lowering medications.
    - ***** The mean reduction in LDL-C with mipomersen (Kynamro) was 25% after 26 weeks of treatment.
- It is not known whether LDL-C is an accurate predictor of clinically meaningful outcomes (e.g. cardiovascular morbidity and mortality) in patients with HoFH.
- There are no head-to-head trials comparing mipomersen (Kynamro) to other treatments for HoFH.

INVESTIGATIONAL CONDITIONS

- Heterozygous Familial Hypercholesterolemia
    - Two small-scale trials have evaluated mipomersen (Kynamro) in heterozygous familial hypercholesterolemia. [6,7]
    - Mipomersen (Kynamro) reduced LDL-C between 21% and 28%; however, due to differential attrition and small number of subjects, the precision of these results is uncertain.
    - While these two trials were suggestive of an effect, it is not clear that mipomersen (Kynamro) results in substantial improvement in clinically meaningful outcomes that outweigh any safety risk. Larger, better designed clinical trials are needed to establish clinical efficacy and safety in this setting.
- Hyperlipidemia / Hypercholesterolemia
    - Several small, randomized, placebo-controlled trials have evaluated mipomersen (Kynamro) in patients with hypercholesterolemia. [8]
    - Mipomersen (Kynamro) reduced LDL-C between 45% and 52%.
    - While suggestive of an effect, it is not clear that mipomersen (Kynamro) results in substantial improvement in clinically meaningful outcomes that outweighs any safety risk. Larger, better designed clinical trials are needed to establish clinical efficacy and safety in this setting.
- In combination with other agents
    - The safety and effectiveness of mipomersen (Kynamro) have not been established in combination with lomitapide (Juxtapid) or evolocumab (Repatha).

Safety

- The most common adverse reactions reported with an incidence of at least 10% include: injection site reactions, flu-like symptoms, nausea, headache, and elevations in liver transaminases. [9]
- Mipomersen (Kynamro) has a boxed warning for risk of elevated transaminases and hepatic steatosis. Liver transaminases should be monitored prior to initiation of mipomersen (Kynamro) and monthly thereafter. Mipomersen (Kynamro) should be discontinued is persistent or significant elevations are observed. [9]
- Because of potential serious side effects, the FDA has initiation a Risk Evaluation and Mitigation (REMS) program to ensure mipomersen (Kynamro) is only used in patients with homozygous familial hypercholesterolemia. [3]

Dosing

- The recommended dose of mipomersen (Kynamro) is 200 mg subcutaneously once weekly. [9]
- The safety and effectiveness of higher doses have not been established.

Cross References
Branded Lipid-Modifying Medications, dru336
Repatha™, evolocumab, dru407
Juxtapid®, lomitapide, dru302

Codes	Number	Description
N/A		

References

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2. Raal, FJ, Santos, RD. Homozygous familial hypercholesterolemia: current perspectives on diagnosis and treatment. *Atherosclerosis*. 2012;223:262-8. PMID: 22398274
3. Kynamro Risk Evaluation and Mitigation Strategy [cited 5/26/2017]; Available from: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM337472.pdf. .
4. Juxtapid Risk Evaluation and Mitigation Strategy [cited 5/26/2017]; Available from: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM333438.pdf.
5. Raal, FJ, Santos, RD, Blom, DJ, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2010;375:998-1006. PMID: 20227758
6. Stein, EA, Dufour, R, Gagne, C, et al. Apolipoprotein B synthesis inhibition with mipomersen in heterozygous familial hypercholesterolemia: results of a randomized, double-blind, placebo-controlled trial to assess efficacy and safety as add-on therapy in patients with coronary artery disease. *Circulation*. 2012;126:2283-92. PMID: 23060426
7. Akdim, F, Visser, ME, Tribble, DL, et al. Effect of mipomersen, an apolipoprotein B synthesis inhibitor, on low-density lipoprotein cholesterol in patients with familial hypercholesterolemia. *The American journal of cardiology*. 2010;105:1413-9. PMID: 20451687
8. Panta, R, Dahal, K, Kunwar, S. Efficacy and safety of mipomersen in treatment of dyslipidemia: A meta-analysis of randomized controlled trials. *Journal of clinical lipidology*. 2015 Mar-Apr;9(2):217-25. PMID: 25911078
9. Kynamro® [Prescribing Information]. Cambridge, MA: Genzyme; March 2015

Revision History

Revision Date	Revision Summary
6/9/2017	Removed mention of evolocumab (Repatha) not being commercially available. No change to intent of coverage criteria.
6/10/2016	No Criteria Changes