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Subject: Mipomersen Sodium (Kynamro®) Injection

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DESCRIPTION:

Homozygous familial hypercholesterolemia (HoFH) is an inherited disorder caused primarily by homozygous mutations in the low-density lipoprotein receptor (LDLR) gene, but also by mutations in apolipoprotein B (Apo-B), proprotein convertase subtilisin/kexin 9 (PCSK9), and (more rarely) autosomal recessive hypercholesterolemia (ARH) adaptor protein.[1] Individuals with HoFH present with severe hypercholesterolemia associated with accumulation of low-density lipoprotein cholesterol (LDL-C) in plasma, tendons, and skin, and exhibit accelerated atherosclerosis, particularly coronary heart disease within the first two decades of life.[1] The prevalence of HoFH is estimated to be 1 case per 1 million persons, whereas the heterozygous form of familial hypercholesterolemia (HeFH) is estimated at 1 case per 500 persons.

Although diagnostic criteria of HoFH is not uniform, Raal, et al have proposed a consistent definition for diagnosis of HoFH that is based on the many similar diagnostic criteria that have been described in medical literature over the last 30 years (Figure 1).[1]

Figure 1

Diagnostic definition of HoFH[1]

Genetic confirmation of 2 mutant alleles at the LDLR, Apo-B, PCSK9, or ARH adaptor protein gene locus

OR

An untreated LDL-C >500 mg/L (13 mmol/L) or treated LDL-C ≥300 mg/dL (7.76 mmol/L) or treated non-HDL-C ≥ 330 mg/dL (8.5 mmol/L) together with either:

- Cutaneous or tendinous xanthoma before age 10 years

OR

- Elevated LDL-C levels before lipid-lowering therapy consistent with HeFH in both parents[a]

[a] Except in the case of ARH

Current treatment options for HoFH include high-dose statin therapy alone or in combination with other cholesterol lowering medications, such as ezetimibe, niacin, bile acid sequestrants, fibrates, and omega-3 fatty acids.[2] Statins, on average, decrease LDL-C 15% (range 0-48%) in individuals with HoFH.[1] When desired reduction in LDL-C is not achieved with pharmacological therapy, LDL-C apheresis may be used; LDL apheresis can reduce LDL-C by more than 50% and can also lower lipoprotein (a), very low density lipoprotein cholesterol (VLDL-C), and triglyceride (TG) levels. However, the procedure is expensive, not readily available, and inconvenient as it has to be carried out every two weeks. Lomitapide, a microsomal triglyceride transfer protein inhibitor, is approved for use as an adjunct to a low-fat diet and other lipid-lowering treatments for individuals with HoFH. Since the drug has only been recently approved, long-term efficacy and safety data is not available.[1]

Mipomersen (Kynamro®) was approved by the U.S. Food and Drug Administration (FDA) on January 30, 2013 as an adjunct to lipid-lowering medications and diet to reduce LDL-C, Apo-B, total cholesterol (TC), and non-high density lipoprotein-cholesterol (non-HDL-C) in individuals with HoFH.[3] Prior to FDA approval, mipomersen received orphan drug status for the treatment of HoFH.[4] Mipomersen inhibits Apo-B protein synthesis.[5,6] This inhibits synthesis and secretion of VLDL and LDL-C.

The safety and efficacy of mipomersen were evaluated in subjects with a confirmed diagnosis of HoFH (n=51) in a 26-week, double blind, placebo-controlled phase III trial.[7] A diagnosis of HoFH was defined by presence of one of the following criteria: (1) Genetic confirmation of HoFH; (2) Untreated TC> 500 mg/dl with xanthoma before 10 years of age; (3) Untreated TC> 500 mg/dl and evidence of HeFH in both parents. Subjects had to be stable on a low-fat diet and pre-existing maximum tolerated lipid-lowering drugs and were not allowed to change their background lipid-lowering therapy for the duration of the study. Subjects were randomized to receive mipomersen 200 mg weekly or placebo.

The primary endpoint was mean percent change in levels of LDL-C from baseline to week 26; secondary endpoints were mean percent change in levels of TC, Apo B, and non-HDL-C. The mean percent change from baseline in LDL-C after 26 weeks of treatment was significantly greater in subjects receiving mipomersen (-24.7%; 95% CI: -31.6, -17.7) compared to placebo (-3.3%; 95% CI: -12.1, 5.5; p=0.0003). A summary of the primary and secondary endpoints is provided in Table 1. Injection site reactions (76% of mipomersen subjects, 24% of placebo subjects) and influenza-like symptoms (29% of mipomersen subjects, 24% of placebo subjects) were the most commonly reported adverse events. Laboratory abnormalities, specifically alanine aminotransferase, were similar between groups.

Table 1. Summary of Results

	Mipomersen Group (n=34)			Placebo Group (n=17)			Difference (95% CI)
	Baseline	Primary Endpoint	Change	Baseline	Primary Endpoint	Change	
LDL-C (mg/dL)	440.1 ± 139	324.3 ± 119.7	-24.7 (-31.6, -17.7)	401.5 ± 142.9	390.0 ± 150.6	-3.3 (-12.1, 5.5)	-21.3 (-32.9, -9.8)
Apo B (mg/dL)	280 ± 80	210 ± 70	-26.8 (-32.7, -20.8)	260 ± 80	250 ± 80	-2.5 (-9.0, 3.9)	-24.2 (-33.8, -14.7)
TC (mg/dL)	501.9 ± 142.9	390.0 ± 123.6	-21.2 (-27.4 -15.0)	459.5 ± 131.3	451.7 ± 142.9	-2.0 (-9.6, 5.6)	-19.2 (-29.5, -9.0)
Non-HDL (mg/dL)	463.3 ± 146.7	347.5 ± 127.4	-24.5 (-31.2, 17.8)	420.8 ± 142.9	409.3 ± 158.3	-2.9 (-11.2, 5.5)	-21.6 (-32.7, -10.5)

Mipomersen has been evaluated in several Phase II studies in subjects with HeFH. The FDA has required a Risk Evaluation and Mitigation Strategy for mipomersen restricting use to HoFH patients only.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Mipomersen therapy does **NOT** meet the definition of medical necessity for members with heterozygous familial hypercholesterolemia or familial hypercholesterolemia (i.e., when the subtype is not specified).

Initiation of mipomersen (Kynamro®) **meets the definition of medical necessity** for members meeting **ALL** of the following criteria:

1. Diagnosis of homozygous familial hypercholesterolemia as defined by meeting **ONE** of the following – documentation from the medical record must be provided:
    a. Genetic confirmation of 2 mutant alleles at the LDLR, Apo-B, PCSK9, or ARH adaptor protein gene locus
    b. Untreated LDL-C >500 mg/L **AND** cutaneous or tendinous xanthoma before age 10 years
    c. Untreated LDL-C >500 mg/L **AND** both parents with documented elevated LDL-C before lipid-lowering therapy consistent with heterozygous familial hypercholesterolemia (e.g., untreated LDL-C >190 mg/dL)
    d. Treated LDL-C ≥300 mg/dL or non-HDL-C ≥ 330 mg/dL **AND** cutaneous or tendinous xanthoma before age 10 years
    e. Treated LDL-C ≥300 mg/dL or non-HDL-C ≥330 mg/dL **AND** both parents with documented elevated LDL-C before lipid-lowering therapy consistent with heterozygous familial hypercholesterolemia (e.g., untreated LDL-C >190 mg/dL)
2. Current treatment, previous intolerance, or contraindication to HMG-CoA reductase inhibitor (statin) therapy at the maximum approved or tolerated dose (e.g., atorvastatin 80 mg/day, rosuvastatin 40 mg/day) for 90 days consecutive therapy
3. Member has had an inadequate response to or has a contraindication to treatment with evolocumab (Repatha®). An inadequate response is defined as continuous treatment for at least 6 months that has **NOT** resulted in **EITHER**:
    a. A 20% or greater reduction in LDL-C as compared to before treatment with evolocumab
    b. A sufficient LDL-C reduction for the member to avoid treatment with LDL apheresis (i.e., LDL-C less than 300 mg/dL)
4. **NO** concurrent use of lomitapide (Juxtapid®) or a PCSK9 inhibitor [e.g., alirocumab (Praluent®) and evolocumab (Repatha®)]
5. Documentation of LDL-C and non-HDL-C levels – measurement must occur within 60 days prior to treatment with mipomersen
6. Age 18 years or older
7. Dose does not exceed 200 mg/week

Duration of approval: 6 months

Continuation of mipomersen **meets the definition of medical necessity** or members meeting **ALL** of the following criteria:

1. Member meets **ONE** of the following:
    a. Authorization/reauthorization has been previously approved by Florida Blue in the past two years for treatment of homozygous familial hypercholesterolemia
    b. Authorization/reauthorization has been previously approved by another health plan in the past two years for treatment of homozygous familial hypercholesterolemia - documentation of a recent (within 90 days prior to authorization request) health plan-paid claim for mipomersen must be provided
    c. Member has previously met all initiation criteria
2. At least **ONE** of the following:
    a. Minimum 20% reduction in LDL-C or non-HDL-C levels since beginning treatment with mipomersen – laboratory documentation must be provided
    b. LDL-C is less than 300 mg/dL or non-HDL-C is less than 330 mg/dL* – laboratory documentation must be provided
3. Current treatment, previous intolerance, or contraindication to HMG-CoA reductase inhibitor (statin) therapy at the maximum approved or tolerated dose (e.g., atorvastatin 80 mg/day, rosuvastatin 40 mg/day) for 90 days consecutive therapy
4. **NO** concurrent use of lomitapide (Juxtapid®) or a PCSK9 inhibitor [e.g., alirocumab (Praluent®) and evolocumab (Repatha®)]
5. Age 18 years or older
6. Dose does not exceed 200 mg/week

Duration of approval: 1 year

*NLA cholesterol thresholds for the initiation of LDL apheresis in patients with HoFH. Treatment to below these thresholds should reduce the need for LDL apheresis.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- 200 mg by subcutaneous injection once weekly; administer injection on the same day every week
- Measure transaminases (ALT, AST), alkaline phosphatase, and total bilirubin prior to initiation of therapy, monthly during the first year of treatment, and at least every three months after the first year
- Measure LDL-C after six months to determine if LDL-C reduction achieved is sufficient to warrant potential risk of liver toxicity

Monitoring Transaminases

ALT or AST ≥ 3x and < 5x ULN

- Confirm elevation with a repeat measurement within one week.
- If confirmed, withhold dose and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR).
- If resuming mipomersen after transaminases resolve to < 3x ULN, consider monitoring liver-related tests more frequently.

ALT or AST >= 5x ULN

- Withhold dosing and obtain additional liver related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR).
- If resuming mipomersen after transaminases resolve to < 3x ULN, monitor liver-related tests more frequently.

Drug Availability

Mipomersen is available as a 200 mg/1 mL solution in either a single-use vial or prefilled syringe.

PRECAUTIONS:

Boxed Warning

- Risk of hepatotoxicity, elevations in transaminases, and increases in hepatic fat; measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating and regularly as recommended
- REMS program – only certified providers may prescribe

Contraindications

- Moderate or severe hepatic impairment (Child-Pugh B or C)
- Active liver disease

Warnings and Precautions

- Injection site reactions
- Flu-like symptoms (e.g., influenza-like illness, pyrexia, chills, myalgia, arthralgia, malaise, fatigue) reported in 30% of individuals and occur within two days after an injection

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding:

J3490	Unclassified drugs

ICD-10 Diagnosis Codes That Support Medical Necessity:

E78.00	Pure hypercholesterolemia, unspecified
E78.01	Familial hypercholesterolemia

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

DEFINITIONS:

None

RELATED GUIDELINES:

Lomitapide (Juxtapid) Oral, 09-J1000-92

PCSK9 Inhibitors, 09-J2000-36

OTHER:

Child-Pugh Classification of Severity of Liver Disease: Using the table below, a total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease).

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin, mg/dL	</= 2	2-3	>3
Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time * Seconds over control * INR	1-3 <1.8	4-6 1.8 – 2.3	>6 >2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

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8. Raal FJ, Santos RD, Blom DJ. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomized, double-blind, placebo-controlled trial. Lancet. 2010; 375: 998-1006.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/13/19.

GUIDELINE UPDATE INFORMATION:

06/15/13	New Medical Coverage Guideline.
06/15/14	Review and revision to guideline; consisting of updating references.
08/15/15	Revision to guideline; consisting of position statement.
11/01/15	Revision: ICD-9 Codes deleted.
10/01/16	Revision to guideline; consisting of updating ICD10 codes
01/01/20	Update to position statement