VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Kynamro® (mipomersen injection for SC use – Genzyme)

TAC APPROVAL DATE: 09/02/2015

LAY CRITERIA EFFECTIVE DATE: 09/14/2015

OVERVIEW

Kynamro, an oligonucleotide inhibitor of apolipoprotein B-100 synthesis, is indicated as an adjunct to lipid modifying therapy and diet to reduce low-density lipoprotein cholesterol (LDL-C), apolipoprotein B, total cholesterol (total-C) and non-high density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).[1] Limitations of use include that the safety and efficacy of Kynamro have not been established in patients with hypercholesterolemia who do not have HoFH. Also, the effect of Kynamro on cardiovascular (CV) morbidity and mortality has not been determined. The use of Kynamro as an adjunct to low-density lipoprotein (LDL) apheresis is not recommended. The recommended dose of Kynamro is 200 mg once weekly (QW) as a subcutaneous (SC) injection. Maximal reduction of LDL-C is observed with Kynamro after approximately 6 months. The first injection administered by the patient or caregiver should be done under the guidance and supervision of an appropriately qualified healthcare professional. The safety and efficacy of Juxtapid have not been established in pediatric patients.

Kynamro has a Boxed Warning regarding the risk of hepatotoxicity.[1] Kynamro may cause elevations in liver transaminases. Also, Kynamro increases hepatic fat (hepatic steatosis) with or without concomitant increases in transaminases. Due to the risk of hepatotoxicity, Kynamro is available only through a Risk Mitigation and Strategy (REMS) Program. Kynamro is a Pregnancy Category B medication. Injection-site reactions are common in patients administered Kynamro (84% of patients). Also, flu-like symptoms, which usually occur within 2 days after an injection, happen in approximately 30% of patients and include one or more of the following: influenza-like illness, pyrexia, chills, myalgia, arthralgia, malaise, or fatigue.

Clinical Data

A pivotal, multinational, randomized (2:1), double-blind, parallel-group, placebo-controlled, published, Phase III, 26-week trial involved 51 patients (aged ≥ 12 years) with HoFH and assessed the efficacy of Kynamro.[1-2] Patients received Kynamro 200 mg SC QW (n = 34) or placebo (n = 17); a 4-week screening phase preceded randomization.[1-2] For patients < 50 kg, the dose of Kynamaro was 160 mg SC QW.[2] A diagnosis of functional HoFH was defined by at least one of the following clinical or laboratory criteria: 1) history of genetic testing confirming two mutated alleles at the low-density lipoprotein receptor (LDLR) gene locus, or 2) documented history of untreated LDL-C > 500 mg/dL and at least one of the following criteria (a) tendinous and/or cutaneous xanthoma prior to age 10 years or (b) documentation of elevated LDL-C > 190 mg/dL prior to lipid-lowering therapy consistent with heterozygous familial hypercholesterolemia (HeFH) in both parents.[1] If data from a parent were unavailable, a history of coronary artery disease (CAD) in a first degree male relative of the parent < 55 years of age or first degree female relative of the parent < 60 years of age was acceptable. At screening, patients were required to be stable and receiving a low-fat diet with a fasting LDL-C ≥ 3.4 mmol/L (~ ≥ 131.5 mg/dL), triglyceride (TG) concentrations < 4.0 mmol/L (~ < 354.3 mg/dL), and body weight ≥ 40 kg.[2] Patients were not permitted to change background lipid-lowering medications during the trial (e.g., statins, cholesterol-

absorption inhibitors, bile-acid sequestrants or nicotinic acid, or a combination thereof). Those receiving LDL apheresis within 8 weeks of the screening visit were excluded due to difficulty in maintaining stable LDL-C concentrations. A significant CV event within 12 weeks of screening was a reason for study exclusion.[2] The primary efficacy endpoint was the percent change in LDL-C from baseline to Week 28.[1] The mean patient age was 32 years (range, 12 years to 53 years);[1-2] seven patients were < 18 years of age.[2] Most of the patients (75%) were Caucasian.[1] Many patients had CV disease at baseline.[2] The mean baseline LDL-C levels for patients receiving Kynamro and placebo were 439 mg/dL (range, 190 mg/dL to 704 mg/dL) and 400 mg/dL (range, 172 mg/dL to 639 mg/dL), respectively;[1-2] approximate baseline total-C levels were 500 mg/dL and 460 mg/dL, respectively.[2] In total, 86% of patients (n = 44/51) had genetic confirmation of LDLR gene mutations.[2] In 98% of patients (n = 50/51), the background therapy of maximally tolerated lipid medication lowering medication included statins.[1] Also, 88% of patients (n = 44/50) were receiving the maximum dose of statin therapy with or without other lipid-lowering medications. In total, 76% of patients (n = 38/50) were also taking at least one other lipid-lowering medication, most commonly Zetia (74%, n = 37/50.[1-2] Patients were not receiving LDL apheresis.[1] ***Results.*** The efficacy endpoint at Week 28 was completed by 82% and 100% of Kynamro- and placebo-treated patients, respectively.[1] AEs led to premature discontinuation in four patients who were all receiving Kynamro. For patients given Kynamro at Week 28, the mean and median percent changes in LDL-C from baseline were -25% ($P < 0.001$) and -19%, respectively.

Guidelines

National Lipid Association (NLA) – Familial Hypercholesterolemia (FH)

In 2011, the NLA published guidelines for the screening, diagnosis, and management of pediatric and adult patients with FH.[3] The guidelines were published prior to the availability of Kynamro. FH encompass a group of genetic defects that cause severe elevations in LDL-C levels, as well as other lipid parameters. FH occurs in approximately 1 in 300 to 500 patients and is present in childhood. There are approximately 1 in one million persons with HoFH and have extreme hypercholesterolemia with rapidly advancing atherosclerosis if untreated. Currently known causes of FH include mutations in LDLR, Apo lipoprotein B (APOB) or proprotein convertase subtilisin/kexin type 9 (PCSK9) genes. Over 1,600 known mutations of the LDLR gene have been documented to cause FH and account for about 85% to 90% of FH cases. Patients with FH may have physical findings such as tendon xanthomas, which may occur at a young age. Individuals with FH are at very high risk of coronary heart disease (CHD) at a premature age. Aggressive lipid modifying therapy is recommended to achieve LDL-C reductions of at least 50%. Both children and adults with LDL-C levels ≥ 190 mg/dL following lifestyle modifications will require medication therapy. Statins are the initial treatment for FH. Higher risk patients may require intensification of drug therapy to achieve the more aggressive treatment goals. Intensification of medication therapy should be considered if LDL-C remains ≥ 160 mg/dL or if an initial 50% reduction in LDL-C is not achieved. Other non-statin therapies that can be considered include Zetia® (ezetimibe tablets), a bile acid sequestrant (e.g., Welchol® [colesevelam tablets and oral suspension), or niacin. Most patients that cannot take a statin will require combination medication therapy. LDL apheresis is recommended in certain circumstances. Patients with HoFH should be managed by a lipid specialist.

European Atherosclerosis Society – Consensus Panel on Familial Hypercholesterolemia

In 2014, the European Atherosclerosis Society published recommendations regarding HoFH.[4] It notes that HoFH is a rare and life-threatening condition characterized by plasma cholesterol levels > 500 mg/dL, extensive xanthomas, and premature clinical atherosclerotic cardiovascular disease (ASCVD). If untreated, patients with extremely elevated LDL-C levels may develop atherosclerosis prior to the second decade of life. The frequency of HoFH is estimated at 1 in one million patients. The diagnosis of HoFH can be done by genetic or clinical criteria. Table 1 notes some criteria used by clinicians.[4]

Table 1. Criteria for the diagnosis of HoFH.[4]

- Genetic confirmation of two mutant alleles at the LDLR, APOB, PCSK9 or LDLRAP1 gene locus; OR
- An untreated LDL-C > 500 mg/dL* or treated LDL-C > 300 mg/dL* together with either 1) cutaneous or tendon xanthoma before the age of 10 years or 2) untreated elevated LDL-C levels consistent with heterozygous FH in both parents.

HoFH – Homozygous familial hypercholesterolemia; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9; LDLRAP1 – Low-density lipoprotein receptor adaptor protein 1; LDL-C – Low-density lipoprotein cholesterol; * These cited LDL-C levels are only indicative and lower levels, especially in children or in untreated patients do not exclude HoFH; FH – Familial hypercholesterolemia.

The Consensus panel strongly recommends that lipid modifying therapy be initiated as early as possible based on evidence that treatment can delay the onset of clinically evident ASCVD.[4] LDL-C targets in HoFH are < 100 mg/dL in adults [< 135 mg/dL in children] or < 70 mg/dL in adults with clinical ASCVD. Statins have been the prominent treatment in HoFH, even among individuals who are receptor negative. Zetia also provides further reduction. Combination therapy may also include other agents such as bile acid sequestrants, niacin and fibrates. LDL apheresis is also utilized and can decrease plasma LDL-C levels by 55% to 70% relative to pre-treatment levels. Regression in cutaneous xanthomas has also been noted. Adverse events (AEs) associated with apheresis include hypotension, abdominal pain, nausea, hypocalcemia, iron-deficiency anemia and allergic reactions. The benefits and AEs of Kynamro were discussed. It is mentioned that in a trial involving patients with HoFH, Kynamro reduced LDL-C at Week 25 by -25%, as well as reduced apolipoprotein B levels and lipoprotein(a). Frequent AEs include injection-site reactions and influenza-like symptoms. Elevations in alanine aminotransaminase (ALT) three times the upper limit of normal was noted in patients, as well as accumulation of liver fat. Kynamro is recommended therapy for HoFH patients following use of the highest tolerated dose of statins, and additional lipid modifying therapies, include LDL apheresis. Another available option for HoFH is Juxtapid® (lomitapide capules).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Kynamro. Because of the specialized skills required for managing patients with HoFH, approval requires Kynamro to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 12 months in duration. The criteria apply to patients initiating therapy and to those currently receiving Kynamro.

Documentation: None required.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kynamro is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. **Homozygous Familial Hypercholesterolemia (HoFH) [Initial and Continuing Therapy].** Approve Kynamro for 12 months if the patient meets the following criteria (A, B, C, D, E and F):
   - **A)** The patient is aged ≥ 18 years; AND
   - **B)** The patient meets one of the following (i, ii, iii or iv):
     - **i.** The patient has had genetic confirmation of two mutant alleles at the low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB), proprotein convertase subtilisin

kexin type 9 (PCSK9) or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene locus; OR

ii. The patient has an untreated low-density lipoprotein cholesterol (LDL-C) level > 500 mg/dL (prior to treatment with antihyperlipidemic agents); OR

iii. The patient has a treated LDL-C level ≥ 300 mg/dL (after treatment with antihyperlipidemic agents but prior to agents such as Repatha™ [evolocumab injection for SC use] or Juxtapid [lomitapide capsules]); OR

iv. The patient has clinical manifestations of HoFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma); AND

C) The patient meets one of the following (i or ii):

i. The patient has tried Repatha (evolocumab injection for SC use) and has had an inadequate response according to the prescribing physician; OR

ii. The patient is known to have two LDL-receptor negative alleles; AND

D) The patient meets one of the following criteria (i or ii):

i. The patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; Crestor® [rosuvastatin tablets] ≥ 20 mg daily [as a single-entity or as a combination product])* for ≥ 8 continuous weeks AND the LDL-C level remains ≥ 70 mg/dL; OR

ii. The patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):

a) The patient experienced statin-related rhabdomyolysis (statin-induced muscle breakdown with signs and symptoms such as muscle pain, weakness, tenderness, acute renal failure and/or elevated creatine kinase [CK] levels [e.g., ≥ 10 times the upper limit of normal]); OR

b) The patient experienced skeletal-related muscle symptoms (e.g., myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness]) and meets both of the following criteria [(1) and (2)]:

(1) The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and Crestor (as single-entity or as combination products); AND

(2) When receiving separate trials of both atorvastatin and Crestor (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and Crestor); AND

E) Kynamro is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders; AND

F) If able to tolerate statins, the patient continues to receive the maximum tolerated dose of a statin while receiving Kynamro.

Kynamro is indicated as an adjunct to lipid-lowering medication and diet to reduce LDL-C, apolipoprotein B, total-C, and non-HDL-C in patients with HoFH. The effects of Kynamro on CV morbidity and mortality has not been determined.[1] The safety and efficacy of Kynamro have not been established in pediatric patients. HoFH is a rare inherited condition in which LDL-C is not adequately removed from the body, resulting in high levels of circulating LDL-C.[3-4] The 2014 HoFH position paper from the Consensus Panel on FH of the European Atherosclerosis Society states the diagnosis of HoFH is made based on genetic or clinical criteria.[4] A definitive diagnosis can be made by genetic confirmation of two mutant alleles at the LDLR, APOB, PCSK9, or LDLRAP1 gene locus. However, in some patients genetic confirmation remains elusive. Historically, HoFH has been commonly diagnosed based on LDL-C levels such as an untreated LDL-C > 500 mg/dL, or a treated

LDL-C ≥ 300 mg/dL. Also confirming the diagnosis is the presence of xanthomas (cutaneous or tendinous) before the age of 10 years or a family history of elevated LDL-C levels consistent with HeFH in both parents.[4] Other clinical manifestations of HoFH include arcus cornea or xanthelasma. Statins are considered the first-line agents in the treatment of HoFH with or without other lipid modifying therapies. High-intensity statins are recommended as low-potency statins are generally inadequate for patients with FH.[3-4] Repatha is indicated for the management of HoFH when used with other LDL-lowering therapies (e.g., statins, Zetia, LDL apheresis).[7] The recommended dose is 420 mg SC once monthly (QM). In patients with HoFH with a baseline LDL-C of 349 mg/dL, the difference between Repatha and placebo in the mean percent LDL-C from baseline in a 12-week study was -31%. It is notable that patients known to have two LDL-receptor negative alleles (little or no residual function) did not respond to Repatha. Repatha is well-tolerated and is not associated with hepatotoxicity.[7] Simvastatin, atorvastatin, and Crestor are indicated for the management of patients with HoFH.[8-10] Zetia is also indicated for use in combination with atorvastatin or simvastatin in patients with HoFH.[11] Two Zetia plus statin combination products are also indicated for use in HoFH (i.e., Vytorin® [ezetimibe/simvastatin tablets] and Liptruzet™ [ezetimibe/atorvastatin tablets]).[12-13] Another agent indicated as an adjunct to lipid-lowering medications and diet to modify lipid parameters (e.g., reduce LDL-C levels) in patients with HoFH is Juxtapid, which also has a REMS program noting hepatotoxicity and hepatic steatosis.[14] Guidelines from the NLA on FH state that HoFH should always be managed by a lipid specialist.[3] The criteria also recognize situations in which patients are unable to take statin therapy (i.e., muscle related AEs) and that rechallenge with a different statin in such scenarios can lead to successful treatment with statin therapy. However, rhabdomyolysis, albeit rare, is a serious event and patients should not be rechallenged with statin therapy.[15-16] The criteria were developed based on nationally-recognized guidelines regarding lipid management, clinical data for Juxtapid and other antihyperlipidemic therapies (e.g., Repatha, statins) as well as the professional opinion of specialized physicians.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Kynamro has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Concurrent use of Kynamro with Juxtapid (lomitapide capsules), Praluent® (alirocumab for SC injection) or Repatha (evolocumab injection for SC use).** Kynamro has not been studied concomitantly with Juxtapid, an oral medication indicated for use in patients with HoFH. Repatha, specifically indicated in HoFH, and Praluent are PCSK9 inhibitors and have not been studied concomitantly with Kynamro therapy.

2. **Use of Kynamro in Patients with Heterozygous Familial Hypercholesterolemia (HeFH).** Kynamro has been studied in patients with HeFH.[5-6] However, the Kynamro prescribing information notes that the safety and effectiveness of Kynamro have not been established in patients with hypercholesterolemia who do not have HoFH.[1] Other options are available for the management of HeFH that possess a better benefit to risk profile (e.g., statins, Praluent, Repatha, Zetia).

3. **Use of Kynamro in Patients with Other Forms of Hyperlipidemia (e.g., Primary Hyperlipidemia, Mixed Dyslipidemia).** Use of Kynamro has not been established in patients with hypercholesterolemia who do not have HoFH.[1]

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date	Lay Criteria Effective Date
New Policy	--	09/02/2015	09/14/2015

* For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx.; TAC – Therapeutic Assessment Committee.