VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Homozygous Familial Hypercholesterolemia – Juxtapid® (lomitapide capsules – Aegerion Pharmaceuticals)

TAC APPROVAL DATE: 10/10/2018

OVERVIEW

Juxtapid, a microsomal triglyceride transfer protein inhibitor, is indicated as an adjunct to a low fat diet and other lipid modifying therapies, including low-density lipoprotein (LDL) apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (total-C), apolipoprotein B, 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 Juxtapid have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH).[1] Also, the effect of Juxtapid on cardiovascular (CV) morbidity and mortality has not been determined. Initiate Juxtapid treatment at 5 mg once daily (QD). Titrate the dose based on safety and tolerability up to the maximum recommended dose of 60 mg daily. Take with water and without food, at least 2 hours after the evening meal because administration with food may increase the risk of gastrointestinal (GI) adverse events (AEs). To reduce the risk of developing a fat-soluble nutrient deficiency due to the mechanism of action of Juxtapid in the small intestine, patients receiving Juxtapid should also receive supplements that contain 400 international units of vitamin E and at least 200 mg linoleic acid, 210 mg of alpha-linolenic acid (ALA), 110 mg of eicosapentaenoic acid (EPA), and 80 mg of docosahexaenoic acid (DHA). The use of Juxtapid is contraindicated with concomitant use of moderate and strong cytochrome P450 (CYP3A4) inhibitors. Also, the recommended maximum dose of Juxtapid is 30 mg daily if given with weak CYP3A4 inhibitors. The safety and efficacy of Juxtapid have not been established in pediatric patients.

Juxtapid has a Boxed Warnings regarding the risk of hepatotoxicity.[1] Juxtapid may cause elevations in liver transaminases. Also, Juxtapid increases hepatic fat (hepatic steatosis) with or without concomitant increases in transaminases. Due to the risk of hepatotoxicity, Juxtapid is available only through a Risk Mitigation and Strategy (REMS) Program. Juxtapid is a Pregnancy Category X medication and may cause fetal harm when given to a pregnant woman based on findings suggesting teratogenicity in animals. Females of reproductive potential should obtain a negative pregnancy test before Juxtapid initiation and should utilize effective contraception during Juxtapid use. Juxtapid is associated with gastrointestinal (GI) adverse events (AEs), which occurred in 93% of patients (n = 27/29). GI AEs included diarrhea (79%), nausea (65%), dyspepsia (38%), vomiting (34%), and abdominal pain (34%). Postmarketing reports regarding severe diarrhea have been associated with use of Juxtapid which have involved hospitalization of patients due to diarrhea-related complications such as volume depletion.

Clinical Data

The efficacy of Juxtapid as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, were assessed in a multinational, single-arm, Phase III, open-label, 78-week pivotal trial that involved adults with HoFH (n = 29).[1-2] A 6-week run-in period was performed to stabilize lipid modifying therapies which included the establishment of an LDL apheresis schedule if applicable. Patients initiated therapy with Juxtapid 5 mg QD for 2 weeks, and then escalated the dose to 10, 20, 40, and 60 mg QD at Weeks 2, 6, 10, and 14, respectively, until an individually determined maximum dose was established based on safety and tolerability. Patients remained at their maximum

dose to the end of the 26-week efficacy phase. For an additional 52 weeks, patients were maintained on Juxtapid therapy (i.e., dose not increased above the maximum tolerated dose) to evaluate long-term safety (Weeks 26 through Week 78) and at that time concomitant lipid modifying therapies, including LDL apheresis, could be changed according to the investigator.[2] The diagnosis of HoFH was defined by the presence of at least one of the following clinical criteria: 1) documented functional mutation(s) in both low-density lipoprotein receptor (LDLR) alleles or alleles know to impact LDL receptor functionality; or 2) skin fibroblast LDL-receptor activity < 20% normal; or 3) untreated total-C > 500 mg/dL and triglyceride (TG) < 300 mg/dL and both parents with documented untreated total-C > 250 mg/dL.[1] The primary efficacy endpoint was the percent change from baseline in LDL-C after 26 weeks of therapy. Other lipid parameters were also assessed. The mean patient age was 30.7 years (range, 18 to 55 years), 16 patients (55%) were men, and most of the patients (86%) were Caucasian.[1-2] All 29 patients were either homozygotes or compound heterozygotes for mutations in the *LDLR* gene or genes impacting LDL-receptor functionality.[2] Concomitant lipid modifying treatments at baseline included one or more of the following: statins (93%), ezetimibe (Zetia®, generics) [76%], nicotinic acid (10%), bile acid sequestrants (3%), and fibrates (3%).[1-2] The main statins used were rosuvastatin tablets and atorvastatin.[2] Apheresis was used as a therapy in 18 patients (62%) and the frequency ranged from weekly to every 6 weeks.[2] ***Results.*** In total, 79% of patients (n = 23/29) completed the efficacy endpoint at Week 26, as well as the 78-week treatment period.[1-2] AEs led to premature discontinuation for five patients.[1] At Week 26, the mean and median percent changes in LDL-C from baseline were -40% ($P < 0.001$) and -50%, respectively, based on the intent-to-treat (ITT) population with last observation carried forward (LOCF) for those who discontinued the trial prematurely.[1-2]

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 Juxtapid. 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 people with HoFH that have extreme hypercholesterolemia with rapidly advancing atherosclerosis if untreated. Currently known causes of FH include mutations in LDLR, apolipoprotein 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 ezetimibe, a bile acid sequestrant (e.g., Welchol® [colesevelam tablets or 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 FH

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. Ezetimibe 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. AEs of apheresis include hypotension, abdominal pain, nausea, hypocalcemia, iron-deficiency anemia and allergic reactions. The benefits and AEs of Juxtapid are discussed. It is mentioned that in a trial involving patients with HoFH, Juxtapid at maximally tolerated doses, in addition to standard of care including LDL apheresis, reduced plasma LDL-C and apolipoprotein B levels by around -50% at Week 26; lipoprotein(a) was reduced by approximately -15% at this timepoint. Frequent AEs include GI symptoms and liver fat accumulation. Elevations in alanine aminotransaminase (ALT) three times the upper limit of normal was noted in approximately one-third of patients. Accumulation of liver fat was also noted. Juxtapid is recommended therapy for HoFH patients following use of the highest tolerated dose of statins, and additional lipid modifying therapies, include LDL apheresis. ~~Another noted agent available for the treatment of HoFH is Kynamro® (mipomersen sodium injection).~~

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Juxtapid. Because of the specialized skills required for managing patients with HoFH, approval requires Juxtapid 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 Juxtapid.

Documentation: None required.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Juxtapid is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Homozygous Familial Hypercholesterolemia (HoFH) [Initial and Continuing Therapy].** Approve Juxtapid for 12 months if the patient meets the following criteria (A, B, C, D, and E):
   - **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 subcutaneous {SC} use]); 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 and 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; 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 (Note: Statin-induced muscle breakdown that is usually associated with markedly elevated creatine kinase [CK] levels [at least 10 times the upper limit of normal], along with evidence of end organ damage which can include signs of acute renal injury [noted by substantial increases in serum creatinine{Scr} levels {a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr}] and/or myoglobinuria [myoglobin present in urine]); 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 rosuvastatin (as single-entity or as combination products); AND
         - **(2)** When receiving separate trials of both atorvastatin and rosuvastatin (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 rosuvastatin); AND

E) Juxtapid 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.

Juxtapid is indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce LDL-C, total-C, apolipoprotein B and non-HDL-C, in patients with HoFH.[1] The effects of Juxtapid on CV morbidity and mortality have not been established.[1] 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, ezetimibe, LDL apheresis).[5] 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.[5] Simvastatin, atorvastatin, and rosuvastatin are indicated for the management of patients with HoFH.[6-8] Ezetimibe is also indicated for use in combination with atorvastatin or simvastatin in patients with HoFH.[9] Ezetimibe/simvastatin tablets are indicated for use in HoFH. 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.[12-13] The criteria were developed based on nationally-recognized guidelines regarding lipid management, clinical data for Juxtapid and other antihyperlipidemic therapies (e.g., Repatha, statins, ezetimibe) as well as the professional opinion of specialized physicians.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Juxtapid 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 Juxtapid with Praluent® (alirocumab for SC injection) or Repatha (evolocumab injection for SC use).** Repatha, specifically indicated in HoFH, and Praluent are PCSK9 inhibitors and have not been studied concomitantly with Juxtapid therapy.

2. **Use of Juxtapid in Patients with Heterozygous Familial Hypercholesterolemia (HeFH).** The safety and effectiveness of Juxtapid have not been establsished in patients with hypercholesterolemia who do not have HoFH, including those with HeFH.[1]

3. **Use of Juxtapid in Patients with Other Forms of Hyperlipidemia (e.g., primary hyperlipidemia, mixed dyslipidemia).** The safety and efficacy of Juxtapid have 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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2. Cuchel M, Meagher EA, du Toit Theron H, et al, for the Phase 3 HoFH Lomitapide Study investigators. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolemia: a single-arm, open-label, phase 3 study. *Lancet*. 2013;381(9860); 40-46. [Supplementary appendix].
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4. Cuchel M, Bruckert E, Ginsberg HN, et al, for the European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia. Homozygous familial hypercholesterolemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolemia of the European Atherosclerosis Society. *Eur Heart J*. 2014;35:2146-2157.
5. Repatha™ injection for subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen; December 2017.
6. Zocor® tablets [prescribing information]. Whitehouse Station, NJ: Merck; February 2018.
7. Lipitor® tablets [prescribing information]. New York, NY: Pfizer; August 2018.
8. Crestor® tablets [prescribing information]. Wilmington, DE: AstraZeneca; August 2017.
9. Zetia® tablets [prescribing information]. Whitehouse Station, NJ: Merck; August 2013.
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12. Rosenson RS, Baker SK, Jacobson TA, et al. An assessment by the statin muscle safety task force: 2014 update. *J Clin Lipidol*. 2014;8:S58-S71.
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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	In applicable sections of the criteria, noted that Crestor is available as a generic and changed the name to rosuvastatin.	09/14/2016
Annual revision	Deleted the criteria for HoFH that states "if able to tolerate statins, the patient continues to receive the maximum tolerated dose of a statin while receiving Juxtapid". Also, revised the note that defines rhabdomyolysis.	10/04/2017
Annual revision	Kynamro no longer available. Therefore, Kynamro was removed from the listing of examples among the diagnostic criteria for HoFH in reference to the criterion that asks if the treated LDL-C level is ≥ 300 mg/dL (after treatment with antihyperlipidemic agents but prior to agents such as Repatha or Kynamro. Additionally, Kynamro was removed from the listing of medications in which Juxtapid cannot be used with concomitantly.	10/10/2018.

* 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; HoFH – Homozygous familial hypercholesterolemia.