PRIOR AUTHORIZATION POLICY

POLICY: Homozygous Familial Hypercholesterolemia – Juxtapid Prior Authorization Policy
- Juxtapid® (lomitapide capsules – Amryt)

REVIEW DATE: 05/08/2024

INSTRUCTIONS FOR USE

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CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Juxtapid, a microsomal triglyceride transfer protein inhibitor, is indicated as an adjunct to a low fat diet and other lipid-lowering treatments, including low-density lipoprotein (LDL) apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol, apolipoprotein B, and non-high-density lipoprotein cholesterol (non-HDL-C) in adults 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). Also, the effect of Juxtapid on cardiovascular (CV) morbidity and mortality have not been determined.

Repatha® (evolocumab subcutaneous injection) and Praluent® (alirocumab subcutaneous injection), two proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, are indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional LDL-C lowering.[2,3] It is notable that patients known to have two LDL-receptor negative alleles (little or no residual function) did not respond or had minimal response to these agents. PCSK9 inhibitors are well tolerated and are not

associated with hepatotoxicity.[2] Simvastatin, atorvastatin, and rosuvastatin are statins that are indicated for the management of patients with HoFH.[4-6] Ezetimibe is also indicated for use in combination with atorvastatin or simvastatin in patients with HoFH.[7] Ezetimibe/simvastatin tablets are indicated for use in HoFH.[8] Evkeeza® (evinacumab-dgnb intravenous infusion), an angiopoietin-like 3 inhibitor, is also indicated as an adjunct to other LDL-C lowering therapies for the treatment of HoFH in patients ≥ 5 years of age.[9]

Disease Overview

Familial hypercholesterolemias, which includes HeFH and HoFH, encompasses a group of genetic defects that causes severe elevations in LDL-C levels, as well as other lipid parameters.[10,11] HoFH impacts approximately 1 in 300,000 to 1,000,000 persons. The condition is most commonly due to impaired functionality of the LDL receptor which leads to a low or absence of clearance of LDL-C from the circulation. Currently known causes of familial hypercholesterolemia include mutations in the LDL receptor, apolipoprotein B, or PCSK9 genes. Patients with familial hypercholesterolemia may have physical findings such as tendon or cutaneous xanthomas, which may occur in childhood. Individuals with familial hypercholesterolemia are at very high risk of atherosclerotic cardiovascular disease (ASCVD) at a premature age. Most guidelines recommended LDL-C targets of < 100 mg/dL for adults and < 70 mg/dL for adults with ASCVD or other risk factors. Statins are the initial treatment for familial hypercholesterolemia. For patients with HoFH, high-intensity statin therapy is recommended, with ezetimibe added as well. Therapy with a PCSK9 inhibitor (e.g., Repatha, Praluent) is usually the next step. Juxtapid can be added onto maximal lipid-lowering therapy and Evkeeza® (evinacumab-dgnb intravenous infusion) may be considered. Combination therapy is required for most patients. LDL apheresis is recommended in certain circumstances. The diagnosis of HoFH can be done by genetic or clinical criteria.[10] An untreated LDL-C > 400 mg/dL is suggestive of HoFH. Patients may have cutaneous or tendon xanthomas before 10 years of age and/or untreated elevated LDL-C levels consistent with HeFH in both parents. In the digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH.

Guidelines

- **American College of Cardiology Expert Consensus Decision Pathway on the Role of Non-statin Therapies (2022):** Specialized therapies, one of which includes Juxtapid, may be needed to control LDL-C in certain patients (e.g., those with HoFH) who have had an inadequate response to statins, with or without ezetimibe, and PCSK9 inhibitors.[12]
- **European Atherosclerosis Society (2023):** Clinical guidance by this organization recommends lipid-lowering therapy be initiated with high-intensity statin therapy and ezetimibe.[11] A PCSK9 inhibitor can be added as well. If patients are not at LDL-C goals, other agents can be alternatives as well (e.g., Juxtapid, Evkeeza). Lipoprotein apheresis may also be considered. The goal is to reduce LDL-C to < 115 mg/dL in children and adolescents, < 70 mg/dL in adults if no major ASCVD risk factors are

present, and < 55 mg/dL if patients have ASCVD or major ASCVD risk factors.

Safety

Juxtapid has a Boxed Warning 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 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.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Juxtapid. All approvals are provided for the duration noted below. A patient who has previously met Initial Therapy criteria for Juxtapid for the requested indication under the Coverage Review Department and is currently receiving Juxtapid is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria has not been met under the Coverage Review Department and the patient is currently receiving Juxtapid, or is restarting Juxtapid, Initial Therapy criteria must be met.

- **Juxtapid® (lomitapide capsules - Amryt)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indication

1. **Homozygous Familial Hypercholesterolemia (HoFH).** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient meets ONE of the following (a, b, or c):
       - **a)** Patient has phenotypic confirmation of homozygous familial hypercholesterolemia; OR

Note: Examples include pathogenic variants at the low-density lipoprotein receptor (LDLR), apolipoprotein B (apo B), proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene.

b) Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level > 400 mg/dL AND meets ONE of the following [(1) or (2)]:
Note: Untreated refers to prior therapy with any antihyperlipidemic agent.

(1) Patient had clinical manifestation of homozygous familial hypercholesterolemia before 10 years of age; OR
Note: Clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma.

(2) At least one parent of the patient had untreated LDL-C levels or total cholesterol levels consistent with familial hypercholesterolemia; OR
Note: An example of familial hypercholesterolemia is an untreated low-density LDL-C level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL.

c) Patient has a treated LDL-C level ≥ 300 mg/dL AND meets ONE of the following [(1) or (2)]:
Note: Treated refers to after therapy with at least one antihyperlipidemic agent. Some examples of antihyperlipidemic agents include statins (e.g., atorvastatin, rosuvastatin, lovastatin, simvastatin, pravastatin), ezetimibe, PCSK9 inhibitors (i.e., Repatha [evolocumab subcutaneous injection], Praluent [alirocumab subcutaneous injection]), and Evkeeza (evinacumab-dgnb intravenous infusion).

(1) Patient had clinical manifestations of homozygous familial hypercholesterolemia before 10 years of age; OR
Note: Examples of clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma.

(2) At least one parent of the patient had untreated LDL-C levels or total cholesterol levels consistent with familial hypercholesterolemia; AND
Note: An example of familial hypercholesterolemia is an untreated LDL-C ≥ 190 mg/dL and/or an untreated total cholesterol > 250 mg/dL.

iii. Patient meets ONE of the following (a or b):

a) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has tried at least one proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor for ≥ 8 continuous weeks; AND
Note: Examples of PCSK9 inhibitors include Repatha (evolocumab subcutaneous injection) and Praluent (alirocumab subcutaneous injection).

(2) LDL-C level after this PCSK9 inhibitor therapy remains ≥ 70 mg/dL; OR

b) Patient is known to have two LDL-receptor negative alleles; AND

iv. Patient meets ONE of the following (a or b):

a) Patient meets ALL of the following [(1), (2), and (3)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single entity or as a combination product]); AND

(2) Patient has tried one high-intensity statin along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND

(3) Low-density lipoprotein cholesterol level after this treatment regimen remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting ONE of the following [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase 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]).

(2) Patient meets ALL of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND

Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products), the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); OR

Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

B) Patient Currently Receiving Juxtapid. Approve if according to the prescriber, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Note: If the patient is currently receiving the requested therapy but has not previously received approval of Juxtapid for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Juxtapid, Initial Therapy criteria must be met.

CONDITIONS NOT COVERED

- **Juxtapid® (lomitapide capsules - Amryt)**

is(are) considered experimental, investigational, or unproven for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

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

2. **Hyperlipidemia.** The safety and efficacy of Juxtapid have not been established in patients with hypercholesterolemia who do not have HoFH.[1]
   Note: This is not associated with homozygous familial hypercholesterolemia and may be referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), mixed dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.

REFERENCES

1. Juxtapid® capsules [prescribing information]. Dublin, Ireland: Amryt; September 2020.
2. Repatha® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; September 2021.
3. Praluent® subcutaneous injection [prescribing information]. Tarrytown, NY: Regeneron; March 2024.
4. Zocor® tablets [prescribing information]. Morgantown, WV; Viatris/Organon; August 2023.
5. Lipitor® tablets [prescribing information]. Morgantown, WV; Viatris; Pfizer; April 2024.
6. Crestor® tablets [prescribing information]. Wilmington, DE: AstraZeneca; July 2023.
7. Zetia® tablets [prescribing information]. Jersey City, NJ: Organon; February 2024.
8. Vytorin® tablets [prescribing information]. Jersey City, NJ: Organon; March 2024.
9. Evkeeza® intravenous infusion [prescribing information]. Tarrytown, NY: Regeneron; March 2023.
10. Cuchel M, Raal FJ, Hegele RA, et al. 2023 update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J*. 2023;44:2277-2291.
11. Raal FJ, Hovingh GK, Catapano AL. Familial hypercholesterolemia treatments: guidelines and new therapies. *Atherosclerosis*. 2018;277:483-492.
12. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *J Am Coll*. 2022;80(14):1366-1418.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	It was added to the Policy Statement that a patient who has previously met initial therapy criteria for Juxtapid for the requested indication under the Coverage Review Department and is currently receiving Juxtapid is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria has not been met under the Coverage Review Department and the patient is currently receiving Juxtapid, or is restarting Juxtapid, initial criteria must be met. In addition, the following change was made:	04/26/2023

	Homozygous Familial Hypercholesterolemia: Requirements were divided to distinguish between initial therapy and patient currently receiving Juxtapid (previously there was only one criteria set). For a patient who is currently receiving Juxtapid and has previously met initial therapy criteria for the requested indication under the Coverage Review Department, only the continuation of therapy criteria has to be met, which was newly developed. The continuation of therapy criteria states that according to the prescribing physician, the patient has experienced a response to therapy with examples provided in a Note.	
Annual Revision	**Policy Statement:** The statement that "the agent is prescribed by or in consultation with a physician who specializes in the condition being treated" was removed. In addition, the following changes were made: **Homozygous Familial Hypercholesterolemia:** For Initial Therapy, the specialist physician requirement was removed. The requirement that the patient has had genetic confirmation by two mutant alleles at the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9, or low-density lipoprotein receptor adaptor protein 1 gene locus was changed to state that the patient has phenotypic confirmation of homozygous familial hypercholesterolemia and the above examples moved to a Note. The diagnostic criterion which stated that the patient has an untreated low-density lipoprotein cholesterol level > 500 mg/dL was changed to > 400 mg/dL. The criterion (which is in two places [those with an untreated low-density lipoprotein cholesterol level > 400 mg/dL and a treated low-density lipoprotein cholesterol level ≥ 300 mg/dL]) that both parents of the patient had untreated low-density lipoprotein cholesterol levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia was changed to state that at least one parent of the patient had untreated low-density lipoprotein cholesterol levels or total cholesterol levels consistent with familial hypercholesterolemia. The related Note that "An example of heterozygous familial hypercholesterolemia in both parents would be if both had an untreated low-density lipoprotein cholesterol level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL" was changed to state "An example of familial hypercholesterolemia is an untreated low-density lipoprotein cholesterol level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL." For a Patient Currently Receiving the Medication, the requirement that the "prescribing physician" notes that the patient has experienced a response to therapy was changed to "prescriber".	05/08/2024

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