LOMITAPIDE

This drug requires a written request for prior authorization. All requests for Juxtapid (lomitapide) require review by a pharmacist prior to final approval.

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA, SEE BELOW)

1. Does the patient have a diagnosis of homozygous familial hypercholesterolemia as determined by meeting ONE of the following criteria:
   - Simon Broome diagnostic criteria (definite) [example: genetic testing consistent with HoFH and pretreatment baseline LDL cholesterol is greater than 190 mg/dL]
   - Cascade screening
   - Dutch Lipid Network criteria with a score at least 6
   - History of untreated cholesterol >500mg/dL (or treated >300mg/dL) and cutaneous xanthoma before age 10
   - Patient has undergone regular apheresis treatments for extremely elevated LDL cholesterol levels with a history of untreated cholesterol >500mg/dL (or treated >300mg/dL).

   If yes, continue to #2.
   If no, do not approve.

   DENIAL TEXT: See the initial denial text at the end of the guideline.

2. Does patient meet the following criteria:
   - Age 18 or older
   - Patient does NOT have any of the following contraindications to Juxtapid (lomitapide): moderate or severe hepatic impairment or active liver disease
   - LDL cholesterol level is at least 160mg/dL while on maximal drug and dietary therapy prior to initiating Juxtapid (lomitapide)
   - Juxtapid is prescribed by, or in consultation with, a cardiologist, endocrinologist or lipidologist.

   If yes, continue to #3.
   If no, do not approve.

   DENIAL TEXT: See the initial denial text at the end of the guideline.

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LOMITAPIDE

INITIAL CRITERIA (CONTINUED)

3. Has patient had a previous trial of a PCSK9 inhibitor (e.g., Praluent (alirocumab) or Repatha (evolocumab))?
   
   If yes, continue to #5.
   If no, continue to #4.

4. Does patient have non-functioning LDL receptors?
   
   If yes, continue to #5.
   If no, do not approve.
   **DENIAL TEXT:** See the initial denial text at the end of the guideline.

5. Is the patient currently taking any of the following strong or moderate CYP3A4 inhibitor medications: boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, voriconazole, amphotericin, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, or verapamil?
   
   If yes, do not approve.
   **DENIAL TEXT:** See the initial denial text at the end of the guideline.
   If no, continue to #6.

6. Will Juxtapid (lomitapide) be used in combination with Zetia (ezetimibe) and at least **ONE** of the following drugs:
   - a high intensity statin (e.g., atorvastatin 40mg or 80mg, rosuvastatin 20mg or 40mg), or
   - a maximally tolerated dose of atorvastatin or rosuvastatin, or
   - a maximally tolerated dose of any statin if patient has previously failed either atorvastatin or rosuvastatin?
   
   If yes, continue to #8.
   If no, continue to #7.
   **DENIAL TEXT:** See the initial denial text at the end of the guideline.

   CONTINUED ON NEXT PAGE
INITIAL CRITERIA (CONTINUED)

7. Will Juxtapid be used in combination with Zetia (ezetimibe) and another LDL-lowering agent (bile acid sequestrant, gemfibrozil or other fibrate, or niacin) given that patient has previously failed at least two statin agents or has absolute contraindication to statins? **Note:** If patient has not previously failed at least two statin agents, documentation must include an absolute contraindication to statin therapy (active, decompensated liver disease; nursing female, pregnancy or plans to become pregnant; hypersensitivity reaction). If patient has previously failed statins, documentation of failure must include the following for each statin:
   - Severe and intolerable adverse effects, with other potential causes ruled out (low vitamin D levels, sudden increase in intense or prolonged physical activity, drug interactions with statins, other metabolic or inflammatory causes), AND
   - Failed rechallenge with a second statin agent, including alternate dosing strategies such as every-other-day statin dosing), AND
   - **ONE** of the following lab values or incidents
     - CK exceeds 10 times upper limit of normal
     - LFTs exceed 3 times upper limit of normal
     - Hospitalization due to severe adverse event such as rhabdomyolysis
     - Severe muscle weakness leading to temporary disability, fall, or inability to use a major muscle group (e.g., unable to stand from a seated position or inability to exit a motor vehicle without assistance.)

If yes, continue to #8.
If no, do not approve.

DENIAL TEXT: See the initial denial text at the end of the guideline.

8. Does the patient have a Lp(a) level greater than 50?

If yes, continue to #9.
If no, **approve for 6 months by HICL with the following quantity limits:**
   - 5mg capsule: #1.5 capsule per day (#45 per 30 days) (allows for titration).
   - 10mg capsule: #1 capsule per day.
   - 20mg capsule: #1 capsules per day.
   - 30mg capsule: #1 capsule per day.
   - 40mg capsule: #1 capsule per day.
   - 60mg capsule: #1 capsule per day.

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LOMITAPIDE

INITIAL CRITERIA (CONTINUED)

9. Is patient currently receiving apheresis, or is not a candidate for apheresis, or does not have access to apheresis?

If yes, approve for 6 months by HICL with the following quantity limits:
- 5mg capsule:  #1.5 capsule per day (#45 per 30 days)(allows for titration)
- 10mg capsule:  #1 capsule per day.
- 20mg capsule:  #1 capsules per day.
- 30mg capsule:  #1 capsule per day.
- 40mg capsule:  #1 capsule per day.
- 60mg capsule:  #1 capsule per day.

If no, do not approve.

DENIAL TEXT: See the initial denial text at the end of the guideline.

INITIAL DENIAL TEXT: Our guideline for LOMITAPIDE requires that the patient is at least 18 years of age, and has a diagnosis of homozygous familial hypercholesterolemia (HoFH) as determined by meeting ONE of the following criteria:
- Simon Broome diagnostic criteria (definite), [example: genetic testing consistent with HoFH and pretreatment baseline LDL cholesterol is greater than 190 mg/dL]
- Cascade screening
- Dutch Lipid Network criteria with a score at least 6
- History of untreated cholesterol >500mg/dL (or treated >300mg/dL) and cutaneous xanthoma before age 10
- Patient has undergone regular apheresis treatments for extremely elevated LDL cholesterol levels with a history of untreated cholesterol >500mg/dL (or treated >300mg/dL).

Additional guideline requirements apply.

(Initial denial text continued on next page)
LOMITAPIDE

INITIAL CRITERIA (CONTINUED)

Approval also requires that **ALL** of the following criteria are met:

- Patient has a LDL cholesterol level of at least 160mg/dL while on maximal drug and
dietary therapy prior to initiating Juxtapid.
- Patient does **NOT** have any of the following contraindications to Juxtapid (lomitapide):
  - moderate or severe hepatic impairment or active liver disease.
- Patient must have had a previous trial of a PCSK9 inhibitor, unless patient has non-
functioning LDL receptors.
- Juxtapid must be prescribed by, or in consultation with, a cardiologist, endocrinologist or
lipidologist.
- Patient is **NOT** using any of the following strong or moderate CYP3A4 medications
  concurrently with Juxtapid (lomitapide): boceprevir, clarithromycin, conivaptan, indinavir,
itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir,
posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir,
voriconazole, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib,
darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, or
verapamil.
- Juxtapid must be used in combination with Zetia (ezetimibe) and **ONE** of the following
drugs:
  - a high intensity statin (e.g., atorvastatin 40mg or 80mg, rosuvastatin 20mg or 40mg), or
  - a maximally tolerated dose of atorvastatin or rosuvastatin, or
  - a maximally tolerated dose of any statin given that if patient has previously failed either
  atorvastatin or rosuvastatin, or
  - an LDL-lowering agent (bile acid sequestrant, gemfibrozil or other fibrate, or niacin)
given that patient has previously failed at least 2 statin agents or has an absolute
contraindication to statins (absolute contraindications include active, decompensated
liver disease; nursing female, pregnancy or plans to become pregnant; hypersensitivity
reaction). For patients unable to take a statin that do not have a contraindication,
documentation of statin trial/failure must include **ALL** of the following for each statin trial:
  - Severe and intolerable adverse effects, with other potential causes ruled out (low
vitamin D levels, sudden increase in intense or prolonged physical activity, drug
interactions with statins, other metabolic or inflammatory causes), AND
  - Failed rechallenge with a second statin agent, including alternate dosing strategies
such as every-other-day statin dosing), AND
  - **ONE** of the following lab values or incidents
    1. CK level > 10,000
    2. LFTs exceed 3 times upper limit of normal
    3. Hospitalization due to severe adverse event such as rhabdomyolysis
    4. Severe muscle weakness leading to temporary disability, fall, or inability to use a
major muscle group (e.g., unable to get up)

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LOMITAPIDE

GUIDELINES FOR USE (CONTINUED)

RENEWAL CRITERIA

1. Is the request for a patient who has had at least 26 weeks of therapy?
   
   If yes, continue to #2.
   If no, do not approve.
   **DENIAL TEXT:** See the renewal denial text at the end of the guideline.

2. Is the patient adherent to Juxtapid (lomitapide) therapy and statin therapy (or Juxtapid (lomitapide) and other lipid-lowering agent if patient is statin intolerant)?
   
   If yes, continue to #3
   If no, do not approve.
   **DENIAL TEXT:** See the renewal denial text at the end of the guideline.

3. Has the patient had a LDL reduction of at least 30% from baseline, at or after 26 weeks of treatment?
   
   If yes, **approve for 12 months by HICL with a quantity limit of #1 capsule per day.**
   If no, do not approve.
   **DENIAL TEXT:** See the renewal denial text at the end of the guideline.

**RENEWAL DENIAL TEXT:** Our guideline for LOMITAPIDE renewal requires that the patient has had at least 26 weeks of therapy, with a LDL reduction of at least 30% from baseline after lomitapide therapy for 26 weeks. Patient must also be adherent to Juxtapid (lomitapide) and statin therapy (or Juxtapid and other lipid-lowering agent, if patient is statin intolerant).

**RATIONALE**
To ensure appropriate use of Juxtapid based on FDA approved indication and current recommendations of experts and treatment guidelines.

Juxtapid should be taken once daily, whole with water and without food, at least 2 hours after evening meal.

Before starting treatment with Juxtapid (lomitapide): 1) measure ALT, AST alkaline phosphatase, and total bilirubin, 2) obtain a negative pregnancy test in females of reproductive potential, 3) initiate a low-fat diet supplying <20% of energy from fat.

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**LOMITAPIDE**

**RATIONALE (CONTINUED)**
The recommended dose titration schedule is detailed below:

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Duration of Administration Before Increase to Next Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg daily</td>
<td>At least 2 weeks</td>
</tr>
<tr>
<td>10 mg daily</td>
<td>At least 4 weeks</td>
</tr>
<tr>
<td>20 mg daily</td>
<td>At least 4 weeks</td>
</tr>
<tr>
<td>40 mg daily</td>
<td>At least 4 weeks</td>
</tr>
<tr>
<td>60 mg daily</td>
<td>Maximum recommended dosage</td>
</tr>
</tbody>
</table>

Dose modifications are recommended with cytochrome P450 3A4 inhibitors, elevated transaminases, and in patients with renal and hepatic impairment.

Juxtapid (lomitapide) is an orally administered first-in-class small-molecule inhibitor of microsomal triglyceride transfer protein (MTP), an intracellular enzyme critical to the assembly of apolipoprotein B (apoB)-containing lipoproteins in enterocytes and hepatocytes. Inhibition of MTP prevents the synthesis of chylomicrons and very-low-density lipoprotein (VLDL), which are precursors to the atherogenic low-density lipoprotein (LDL) particle. HoFH is a serious, rare genetic disease that impairs the function of the receptor responsible for removing LDL-C from the body. A loss of LDL receptor function results in extreme elevation of blood cholesterol levels resulting in premature and progressive atherosclerosis. In the United States, HoFH occurs in approximately one in one million individuals. For those with HoFH, heart attacks and death often occur before age 30. Juxtapid works by impairing the creation of the lipid particles that ultimately give rise to LDL. Although statins are the pharmacological agents of choice, individuals with HoFH have absent or dysfunctional LDL-receptors (LDL-R), which substantially attenuates the efficacy of statins. Extracorporeal removal of LDL-C (plasmapheresis or LDL apheresis) is the treatment of choice, but this therapy is not widely available, requires repeat procedures on a weekly or biweekly basis for life, and can be complicated by vascular access difficulties.

The FDA is requiring three postmarketing studies for Juxtapid: an animal study to evaluate the potential for toxicity in children and teens; a long-term registry of patients with HoFH treated with Juxtapid to determine the long-term safety; and an enhanced pharmacovigilance program to monitor reports of malignancy, teratogenicity, and hepatic abnormalities. Juxtapid is currently available through limited distribution and has a REMS program.

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RATIONALE (CONTINUED)
The safety and effectiveness of Juxtapid as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, were evaluated in a multinational, single-arm, open-label, 78-week trial involving 29 adults with HoFH. Concomitant lipid-lowering treatments at baseline included one or more of the following: statins (93%), ezetimibe (76%), nicotinic acid (10%), bile acid sequestrant (3%), and fibrate (3%); 18 (62%) were receiving apheresis. Concomitant lipid-lowering regimens and LDL apheresis schedules were not to be altered during the first 26 weeks of the trial. For those receiving LDL apheresis, efficacy was to be evaluated on the basis of pre-apheresis lipid levels.

After a six-week run-in period to stabilize lipid-lowering treatments, including the establishment of an LDL apheresis schedule if applicable, Juxtapid was initiated at 5 mg daily and titrated to daily doses of 10 mg, 20 mg, 40 mg, and 60 mg at weeks 2, 6, 10, and 14, respectively, based on tolerability and acceptable levels of transaminases. The maximum tolerated doses during the efficacy period were 5 mg (10%), 10 mg (7%), 20 mg (21%), 40 mg (24%), and 60 mg (34%). Patients were instructed to maintain a low-fat diet (<20% calories from fat) and to take dietary supplements that provided approximately 400 international units vitamin E, 210 mg alpha-linolenic acid (ALA), 200 mg linoleic acid, 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA) per day. After efficacy was assessed at Week 26, patients remained on Juxtapid for an additional 52 weeks to assess long-term safety. During this safety phase, the dose of Juxtapid was not increased above each patient’s maximum tolerated dose established during the efficacy phase, but changes to concomitant lipid-lowering treatments were allowed.

Twenty-three (79%) patients completed the efficacy endpoint at Week 26, all of whom went on to complete 78 weeks of treatment. The primary efficacy endpoint was percent change in LDL-C from baseline to Week 26. At Week 26, the mean and median percent changes in LDL-C from baseline were -40% (paired t-test p<0.001) and -50%, respectively, based on the intent-to-treat population with last observation carried forward (LOCF) for patients who discontinued prematurely. Mean LDL-C was 336mg/dl at baseline despite subjects taking maximally tolerated lipid-lowering therapy. At week 26/LOCF, the mean LDL-C was 190mg/dl.

Of the 29 subjects who started the trial, 20 (69%) achieved ≥15% reduction in LDL-C from baseline to week 26/LOCF, 19 (66%) achieved ≥25%, and 14 (48%) achieved ≥50%. Eight (35%) of the 23 subjects who completed the efficacy period had an LDL-C level <100mg/dl at week 26, with one subject having a level <70mg/dl.

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RATIONALE (CONTINUED)
The Juxtapid label contains a boxed warning describing the risk of hepatotoxicity with Juxtapid therapy, including elevations in transaminases levels and the risk of hepatic steatosis. Because of the risk of hepatotoxicity, Juxtapid is available only through a restricted program called the Juxtapid REMS Program that includes prescriber and pharmacy certification and documentation of safe-use conditions consisting of a prescription authorization form that will be required to accompany each new prescription.

Contraindications to therapy with Juxtapid include pregnancy, concomitant use with strong or moderate CYP3A4 inhibitors, and concomitant use with strong or moderate CYP3A4 inhibitors. Warnings and precautions include embryo-fetal toxicity, and gastrointestinal adverse reactions that could affect absorption of concomitant oral medications. Juxtapid increases plasma level concentrations of warfarin, simvastatin and lovastatin and P-gp substrates, dosing adjustments are recommended.

The most common adverse reactions were gastrointestinal, reported by 27 (93%) of 29 patients. Adverse reactions reported by ≥8 (28%) patients in the HoFH clinical trial included diarrhea, nausea, vomiting, dyspepsia, and abdominal pain. Other common adverse reactions, reported by 5 to 7 patients (17-24%), included weight loss, abdominal discomfort, abdominal distension, constipation, flatulence, increased ALT, chest pain, influenza, nasopharyngitis, and fatigue. Five (17%) of the 29 patients with HoFH that participated in the clinical trial discontinued treatment due to an adverse reaction.

FDA APPROVED INDICATIONS
Juxtapid is indicated as an adjunct to a low-fat diet and other lipid lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apoB), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

Limitations of Use
• The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH.
• The effect of JUXTAPID on cardiovascular morbidity and mortality has not been determined.

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REFERENCES


<table>
<thead>
<tr>
<th>Library</th>
<th>Commercial</th>
<th>NSA</th>
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<td>Yes</td>
<td>Yes</td>
<td>No</td>
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</tbody>
</table>

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