Lomitapide (Juxtapid®)
Criteria for Use
March 2014

VHA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient. Individual cases that are exceptions to the exclusion and inclusion criteria should be adjudicated at the local facility according to the policy and procedures of its P&T Committee and Pharmacy Services.

The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx for further information.

Exclusion Criteria If one box below is checked, the patient should NOT receive lomitapide.

- Contraindications:
  - Pregnancy (Category X)
  - Concomitant administration of moderate or strong inhibitors of CYP 3A4 (see footnote; list is not all-inclusive)
  - Patients with moderate or severe liver impairment (e.g., Child-Pugh category B or C) and patients with active liver disease; including those with unexplained persistent elevation of serum transaminases (≥3 x ULN)
  - Patients without a diagnosis of homozygous familial hypercholesterolemia (HoFH)

Inclusion Criteria All boxes must be checked in order to meet criteria to receive lomitapide

- Provider is certified to prescribe lomitapide
- Diagnosis of homozygous familial hypercholesterolemia (HoFH):
  - Confirmed with genetic testing (mutation in LDL receptor: true homozygote or double heterozygote), OR
  - Untreated LDL of >500 mg/dL OR
  - Receiving maximal treatment with lipid-lowering therapy and LDL >300 mg/dL (adherence is confirmed), AND
  - Physical findings including: tendon xanthomas at any age, arcus corneae in patients <45 years or tuberous xanthomas or xanthelasma in patients <20 years.
- Patient has been educated regarding the need to follow a low fat diet and is willing and able to follow a diet consisting of <20% of daily calories from fat.
- Receiving LDL apheresis, if a candidate for therapy and if therapy is accessible
- Negative pregnancy test confirmed, if applicable

Dosage and Administration (refer to prescribing information for more detailed information)

http://juxtapid.com/sites/default/files/downloads/Prescribing_Information.pdf

Recommended Dose Titration Schedule*

<table>
<thead>
<tr>
<th>Lomitapide Dose</th>
<th>Duration of Administration prior to Considering Dose Titration</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 dose</td>
</tr>
</tbody>
</table>

*Doses titrated based upon safety and tolerance to therapy

Dosing in Special Populations

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>Maximum Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>End stage renal disease on dialysis</td>
<td>40 mg daily</td>
</tr>
<tr>
<td>End stage renal disease, not on dialysis</td>
<td>Unknown</td>
</tr>
<tr>
<td>Other stages of renal impairment</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

| Liver Impairment | |
|------------------||

March 2014
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Lomitapide (Juxtapid) Criteria

- Mild impairment (Child-Pugh A)
- Moderate-Severe Impairment (Child-Pugh B-C)
- 40 mg daily
- Contraindicated

**Concomitant CYP 3A4 inhibitors**
- Weak inhibitors (see prescribing information for list)
- Moderate or strong inhibitors (see prescribing information for list)
- 30 mg daily
- Contraindicated

**Pregnancy**
- Contraindicated

**Nursing Mothers**
- Decision to discontinue nursing or lomitapide therapy

**Administration**
- To minimize the risk for adverse gastrointestinal adverse events: 1) Titrate the lomitapide dose as recommended, 2) initiate a low fat diet (<20% of total daily calories as fat) and 3) instruct the patient to take lomitapide at least two hours after the evening meal with a glass of water.
- Lomitapide can reduce absorption of fat-soluble vitamins and fatty acids, therefore daily supplements containing at least 400 international units of Vitamin E, 200 mg linoleic acid, 210 mg alpha-linoleic acid (ALA), 110 mg, eicosapentaenoic acid (EPA) and 80 mg docosahexaenoic acid (DHA) should be taken to prevent deficiencies.

**Monitoring**
- Prior to starting lomitapide, baseline liver function tests (LFTs) (e.g., ALT, AST, alkaline phosphatase and total bilirubin) are recommended.
- LFTs (at least ALT and AST) should be done prior to each dose escalation or at least monthly for the first year.
- After the first year, LFTs should be measured every 3 months and/or prior to dose escalation.
- If LFTs become abnormal, follow the recommended steps for dose adjustment and monitoring:

<table>
<thead>
<tr>
<th>ALT or AST Elevation</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| > 3x ULN and < 5 x ULN* | • Repeat test in 1 week to confirm  
|                       | • If confirmed, reduce dose and obtain other LFTs if not already done (alkaline phosphatase, total bilirubin, INR)  
|                       | • Repeat tests weekly and hold lomitapide if signs or symptoms of liver function impairment (e.g., increased bilirubin or INR or symptoms including nausea, vomiting abdominal pain, fever, jaundice, lethargy or flu-like syndrome), if transaminases rise above 5X ULN or do not fall below 3X ULN within 4 weeks. If abnormalities persist or worsen, investigate probable cause.  
|                       | • If restarting lomitapide after resolution of elevated LFTs, to <3X ULN, consider lowering dose and monitoring LFTs more frequently |
| ≥ 5x ULN*            | • Stop therapy, obtain other LFTs if not already done (alkaline phosphatase, total bilirubin, INR)  
| *Based upon an ULN of approximately 30-40 IU/L | • Investigate the probable cause  
|                       | • If restarting lomitapide after resolution of elevated LFTs to <3X ULN, consider lowering dose and monitoring LFTs more frequently |

*Table adapted from prescribing information*

LFTs=liver function tests, INR=international normalized ratio, ULN=upper limit of normal
Lomitapide (Juxtapid) Criteria

Issues for Consideration

- **BECAUSE OF THE POTENTIAL RISK FOR LIVER INJURY, USE OF LOMITAPIDE IS RESTRICTED TO ONLY THOSE PATIENTS DIAGNOSED WITH HOFH. THERE ARE MULTIPLE WAYS THE DIAGNOSIS OF HOFH CAN BE MADE, INCLUDING:**
  - Confirmed with generic testing
  - Extremely high LDL (e.g., untreated LDL >500 mg/dL OR maximally treated LDL of >300 mg/dL [on lipid lowering therapy including statins, if tolerated, and LDL apheresis] and physical findings including tendon xanthomas at any age, arcus corneae in patients <45 years or tuberous xanthomas or xanthelasma in patients <20 years.
- Lomitapide has been studied in very few patients with HoFH. It is possible that uncommon, severe adverse events were not identified during the completed trials because of the small numbers of patients.
- Safety data beyond 78 weeks is limited.
- Lomitapide can increase transaminases and increase hepatic steatosis. Although there have not been reported cases of liver impairment or liver failure in patients taking lomitapide, there is concern that steatohapatitis could develop in association with lomitapide and gradually progress to cirrhosis. Because of the risk for liver injury developing in patients receiving lomitapide, the FDA has instituted a Risk Evaluation and Mitigation Strategy (REMS) program restricting its prescribing and distribution to only certified providers and pharmacies.
- Patients should have baseline LFTs (ALT, AST, alkaline phosphatase and total bilirubin) performed prior to initiation of lomitapide. ALT and AST should be measured prior to each dose escalation or monthly for the first year. After the first year, ALT and AST should be measured every 3 months and/or prior to each dose escalation. (See the Dosing and Administration section for recommendations for patients with transaminase elevation during lomitapide therapy)
- Patients should be instructed to limit alcohol-containing beverages to no more than one per day. In the clinical trial, those consuming more alcohol than recommended had a higher risk for transaminase elevation.
- To minimize the risk for adverse gastrointestinal events, lomitapide should be initiated at a low dose and gradually titrated upward, as tolerated. A low fat diet (<20% of daily calories as fat) should be instituted and lomitapide taken at least 2 hours after the evening meal with a glass of water.
- Lomitapide should not be used in patients with severe hypercholesterolemia or statin intolerant patients who do not have HoFH. The risk/benefit profile is unfavorable in these patients because of the potential for liver injury.
- Lomitapide can interfere with absorption of fat soluble vitamins and fatty acids therefore daily supplements containing at least 400 international units of Vitamin E, 200 mg linoleic acid, 210 mg alpha-linoleic acid (ALA), 110 mg, eicosapentaenoic acid (EPA) and 80 mg docosahexaenoic acid (DHA) should be taken to prevent deficiencies.
- Lomitapide is metabolized through CYP 3A4 and is vulnerable to interactions involving CYP 3A4 inhibitors. Use of lomitapide is contraindicated with moderate and strong inhibitors of CYP 3A4. See prescribing information for dose adjustment of lomitapide with weak CYP 3A4 inhibitors.
- Grapefruit juice should not be consumed by patients taking lomitapide.
- Lomitapide is an inhibitor of P-glycoprotein (P-gp) and may increase absorption of P-gp substrates. See prescribing information for dose adjustment.
- Lomitapide can increase simvastatin exposure and therefore patients receiving lomitapide should receive only ½ the usual maximum dose of simvastatin (e.g., 20 mg in those previously on simvastatin 40 mg and 40 mg in those previously tolerating 80 mg for at least one year without evidence of muscle toxicity). Since lovastatin is metabolized similarly, halving the dose of lovastatin should be considered (e.g., 40 mg if previously receiving 80 mg, etc.). No dose adjustments are listed for other statins.
- Lomitapide can increase INR in patients taking warfarin. Therefore, close monitoring of INR is indicated in patients taking warfarin and starting lomitapide or with lomitapide dose escalation.

Renewal Criteria

- Patient is tolerating lomitapide and is adherent to therapy

March 2014
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Lomitapide (Juxtapid) Criteria

- Meaningful reduction in LDL (>30-40%)
- LFT monitoring is being conducted as recommended
- Patient is following a low fat diet consisting of <20% of daily calories from fat
- Patient is not pregnant or planning to become pregnant
- Medication list is reviewed for drug-drug interactions
- Patient is taking appropriate supplementation with fat-soluble vitamins and fatty acids (as listed in the issues for consideration)

Moderate CYP 3A4 Inhibitors: amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil Strong CYP 3A4 Inhibitors: bocepravir, clarithromycin, conivaptan, indinavir, intraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole (Lists may not be all inclusive)

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