**09-J1000-92**

**Original Effective Date: 06/15/13**

**Reviewed: 05/14/14**

**Revised: 01/01/20**

# Subject: Lomitapide (Juxtapid®) Oral

**THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.**



## DESCRIPTION:

Homozygous familial hypercholesterolemia (HoFH) is an inherited disorder caused primarily by homozygous mutations in the low-density lipoprotein receptor (LDLR) gene, but also by mutations in apolipoprotein B (Apo-B), proprotein convertase subtilisin/kexin 9 (PCSK9), and (more rarely) autosomal recessive hypercholesterolemia (ARH) adaptor protein.[1] Individuals with HoFH present with severe hypercholesterolemia associated with accumulation of low-density lipoprotein cholesterol (LDL-C) in plasma, tendons, and skin, and exhibit accelerated atherosclerosis, particularly coronary heart disease within the first two decades of life.[1] The prevalence of HoFH is estimated to be 1 case per 1 million persons, whereas the heterozygous form of familial hypercholesterolemia (HeFH) is estimated at 1 case per 500 persons.

Although diagnostic criteria of HoFH is not uniform, Raal et al. have proposed a consistent definition for diagnosis of HoFH that is based on the many similar diagnostic criteria that have been described in medical literature over the last 30 years (Figure 1).[1]

### Figure 1

**Diagnostic definition of HoFH**[1]

Genetic confirmation of 2 mutant alleles at the LDLR, Apo-B, PCSK9, or ARH adaptor protein gene locus

**OR**

An untreated LDL-C >500 mg/L (13 mmol/L) or treated LDL-C ≥300 mg/dL (7.76 mmol/L) or treated non-HDL-C ≥ 330 mg/dL (8.5 mmol/L) together with either:

- Cutaneous or tendinous xanthoma before age 10 years

**OR**

- Elevated LDL-C levels before lipid-lowering therapy consistent with HeFH in both parents[a]

[a] Except in the case of ARH

Current treatment options for HoFH include high-dose statin therapy alone or in combination with other cholesterol lowering medications, such as ezetimibe, niacin, bile acid sequestrants, fibrates, and omega-3 fatty acids.[2] Statins, on average, decrease LDL-C 15% (range 0-48%) in individuals with HoFH.[1] When desired reduction in LDL-C is not achieved with pharmacological therapy, LDL-C apheresis may be used; LDL apheresis can reduce LDL-C by more than 50% and can also lower lipoprotein (a), very low density lipoprotein cholesterol (VLDL-C), and triglyceride (TG) levels. However, the procedure is expensive, not readily available, and inconvenient as it has to be carried out every two weeks. Mipomersen, a second-generation antisense oligonucleotide that is designed to inhibit Apo-B protein synthesis, is approved for use as an adjunct to a low-fat diet and other lipid-lowering treatments for individuals with HoFH. Since the drug has only been recently approved, long-term efficacy and safety data is not available.[1]

Lomitapide (Juxtapid™) was approved by the U.S. Food and Drug Administration (FDA) on December 21, 2012 as an adjunct to lipid-lowering medications and diet to reduce LDL-C, Apo-B, total cholesterol (TC), and non-high density lipoprotein-cholesterol (non-HDL-C) in individuals with HoFH.[3] Prior to FDA approval, lomitapide received orphan drug status for the treatment of HoFH.[4] Lomitapide inhibits the microsomal triglyceride transport protein (MTP), a key protein in the assembly and secretion of Apo B-containing lipoproteins in the liver and intestine.[5,6] This inhibits synthesis of VLDL and chylomicrons leading to reduced levels of plasma LDL-C.

The safety and efficacy of lomitapide were evaluated in subjects with a confirmed diagnosis of HoFH (n=29) in a single arm, open label Phase III study by Cuchel et al.[7] A diagnosis of HoFH was defined by presence of one of the following criteria: (1) Untreated TC> 500 mg/dl and TG <300 mg/dl and both parents have documented TC > 250 mg/dl; (2) Documented functional mutation(s) in both LDL receptor alleles and alleles of other genes known to affect LDL receptor functionality (3) Skin fibroblast LDL receptor activity <20% of the normal. Prior to initiating therapy with lomitapide, subjects were stabilized on their current lipid lowering therapy for six weeks and continued treatment throughout the duration of the study. Subjects were administered lomitapide 5 mg daily for a period of 12 weeks. At the end of 12 weeks, lomitapide was increased every four weeks (10, 20, 40, 60 mg/day) or until a maximum dose was reached on the basis of safety and tolerability.

The primary endpoint was mean percent change in levels of LDL-C from baseline to week 26; secondary endpoints were mean percent change in levels of TC, Apo B, non-HDL-C, VLDL-C, and TG. The median dose was 40 mg daily. The mean percent change from baseline in LDL-C after 26 weeks of treatment was -40% (95% CI: -52, -28) (p<0.001). A summary of the primary and secondary endpoints is provided in Table 1. In the study, subjects continued to receive lomitapide through week 26 to 78 for safety assessment. Adverse event related treatment discontinuations occurred in 17% of subjects (5/29); these were due to diarrhea (2 subjects; 7%) and abdominal pain, nausea, gastroenteritis, weight loss, headache, and difficulty controlling INR on warfarin (1 subject each; 3%). Adverse events related to the gastrointestinal system were the most common and were reported by 93% of subjects in the study (27/29). Almost 1/3 of subjects (34% [10/29]) had at least one elevation in ALT and/or AST greater than 3 times the ULN.

## Table 1. Summary of Results[7]

| | Baseline | Week 26 | Mean % Reduction (95% CI) |
|---|---|---|---|
| LDL-C (mg/dL) | 336 ± 114 | 190 ± 104 | 40 (52, 28), p<0.001 |
| TC (mg/dL) | 430 ± 135 | 258 ± 118 | 36 (47, 26), p<0.001 |

| | | | |
|---|---|---|---|
| Apo B (mg/dL) | 259 ± 80 | 148 ± 74 | 39 (51, 28), p<0.001 |
| Non-HDL-C (mg/dL) | 386 ± 132 | 217 ± 113 | 40 (51, 29), p<0.001 |
| VLDL-C (mg/dL) | 21 ± 10 | 13 ± 9 | 29 (51, 7), p=0.012 |
| TG (mg/dL)a | 92 [72, 128] | 57 [36, 78] | 29 (51, 8), p=0.009 |
| [a] Median values with interquartile range and median % change presented for TG. | | | |

Lomitapide has been evaluated in three Phase II studies in non-FH patients. Although these studies evaluated lomitapide at considerably lower doses than currently approved and were of a short duration (4 to 12 weeks), all three trials demonstrated a reduction in LDL-C. The FDA has required a Risk Evaluation and Mitigation Strategy for lomitapide restricting use to HoFH patients only.

## POSITION STATEMENT:

**Comparative Effectiveness**

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Lomitapide does **NOT** meet the definition of medical necessity for members with heterozygous familial hypercholesterolemia or familial hypercholesterolemia (i.e., when the subtype is not specified).

Initiation of lomitapide (Juxtapid®) **meets the definition of medical necessity** for members meeting the **ALL** of the following criteria:

1. Diagnosis of homozygous familial hypercholesterolemia as defined by meeting **ONE** of the following – documentation from the medical record must be provided:
    a. Genetic confirmation of 2 mutant alleles at the LDLR, Apo-B, PCSK9, or ARH adaptor protein gene locus
    b. Untreated LDL-C >500 mg/L **AND** cutaneous or tendinous xanthoma before age 10 years
    c. Untreated LDL-C >500 mg/L **AND** both parents with documented elevated LDL-C before lipid-lowering therapy consistent with heterozygous familial hypercholesterolemia (e.g., untreated LDL- C > 190 mg/dL)
    d. Treated LDL-C ≥300 mg/dL or non-HDL-C ≥330 mg/dL **AND** cutaneous or tendinous xanthoma before age 10 years
    e. Treated LDL-C ≥300 mg/dL or non-HDL-C ≥330 mg/dL **AND** both parents with documented elevated LDL-C before lipid-lowering therapy consistent with heterozygous familial hypercholesterolemia (e.g., untreated LDL-C >190 mg/dL)
2. Current treatment, previous intolerance, or contraindication to HMG-CoA reductase inhibitor (statin) therapy at the maximum approved or tolerated dose (e.g., atorvastatin 80 mg/day, rosuvastatin 40 mg/day) for 90 days consecutive therapy
3. **NO** current use of strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole)

4. **NO** current use of moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil)
5. Member has had an inadequate response to, or has a contraindication to treatment with evolocumab (Repatha®). An inadequate response is defined as continuous treatment for at least 6 months that has NOT resulted in EITHER:
    a. A 20% or greater reduction in LDL-C as compared to before treatment with evolocumab
    b. A sufficient LDL-C reduction for the member to avoid treatment with LDL apheresis (i.e., LDL-C less than 300 mg/dL)
6. **NO** concurrent use of mipomersen (Kynamro®) or a PCSK9 inhibitor [e.g., alirocumab (Praluent®) and evolocumab (Repatha®)]
7. Documentation of LDL-C and non-HDL-C levels – measurement must occur within 60 days prior to treatment with lomitapide
8. Age 18 years or older
9. Dose does not exceed 60 mg/day and is obtained using the fewest number of capsules possible

Duration of approval: 6 months

Continuation of lomitapide **meets the definition of medical necessity** for members meeting **ALL** of the following criteria:

1. Member meets **ONE** of the following:
    a. Authorization/reauthorization has been previously approved by Florida Blue in the past two years for treatment of homozygous familial hypercholesterolemia
    b. Authorization/reauthorization has been previously approved by another health plan in the past two years for treatment of homozygous familial hypercholesterolemia - documentation of a recent (within 90 days prior to authorization request) health plan-paid claim for lomitapide must be provided
    c. Member has previously met all initiation criteria
2. At least **ONE** of the following:
    a. Minimum 20% reduction in LDL or non-HDL-C since beginning treatment with lomitapide – laboratory documentation must be provided
    b. LDL-C is less than 300 mg/dL or non-HDL-C is less than 330 mg/dL* - laboratory documentation must be provided
3. Current treatment, previous intolerance, or contraindication to HMG-CoA reductase inhibitor (statin) therapy at the maximum approved or tolerated dose (e.g., atorvastatin 80 mg/day, rosuvastatin 40 mg/day) for 90 days consecutive therapy
4. **NO** current use of strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole)
5. **NO** current use of moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil)
6. **NO** concurrent use of mipomersen (Kynamro®) or a PCSK9 inhibitor [e.g., alirocumab (Praluent®) and evolocumab (Repatha®)]

7. Age 18 years or older
8. Dose does not exceed 60 mg/day

Duration of approval: 1 year

*NLA cholesterol thresholds for the initiation of LDL apheresis in patients with HoFH. Treatment to below these thresholds should reduce the need for LDL apheresis.

## DOSAGE/ADMINISTRATION:

**THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE**.

**FDA-approved**

- Initiate at 5 mg once daily, then titrate based on acceptable safety and toxicity; see Table 2 for dose escalation schedule.
- Measure transaminases (ALT, AST), alkaline phosphatase, and total bilirubin prior to initiation of therapy, before any increase in dose, monthly during the first year of treatment, and at least every three months after the first year
- Lomitapide may cause deficiency of fat-soluble nutrients due to its mechanism of action in the small intestine; daily supplements that contain 400 IU vitamin E and at least 200 mg linoleic acid, 210 mg alpha-linolenic acid, 110 mg eicosapentaenoic acid, and 80 mg docosahexaenoic acid are recommended in those taking lomitapide.

### Table 2. Dose Escalation Schedule for Lomitapide

| Dose | Duration of administration before titrating dose to next dosage level |
|---|---|
| 5 mg daily | At least 2 weeks |
| 10 mg daily | At least 4 weeks |
| 20 mg daily | At least 4 weeks |
| 40 mg daily | At least 4 weeks |
| 60 mg daily | Maximum recommended dose |

**Dose Adjustments**

Hepatic Impairment

- Mild hepatic impairment (Child-Pugh A): Do not exceed 40 mg/day
- Moderate hepatic impairment (Child-Pugh B): Contraindicated
- Severe hepatic impairment (Child-Pugh C): Contraindicated

Renal Impairment

- Endstage renal disease receiving hemodialysis: Do not exceed 40 mg/day
- Mild/Moderate/Severe renal impairment: No data, but may experience ≥ 50% increase in lomitapide exposure

Concomitant use of CYP3A4 Inhibitors – See Appendix for list of CYP3A4 inhibitors

- Weak CYP3A4 inhibitor: Do not exceed 30 mg/day
- Moderate CYP3A4 inhibitor: Contraindicated
- Strong CYP3A4 inhibitor: Contraindicated

**Monitoring Transaminases**

ALT or AST ≥ 3x and < 5x ULN

- Confirm elevation with a repeat measurement within one week.
- If confirmed, reduce the dose and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR).
- Repeat tests weekly and withhold dosing if there are signs of abnormal liver function (increase in bilirubin or INR), if transaminase levels rise above 5x ULN, or if transaminase levels do not fall below 3x ULN within approximately 4 weeks.
- If resuming lomitapide after transaminases resolve to < 3x ULN, consider reducing the dose and monitor liver-related tests more frequently.

ALT or AST >= 5x ULN

- Withhold dosing and obtain additional liver related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR).
- If resuming lomitapide after transaminases resolve to < 3x ULN, reduce the dose and monitor liver-related tests more frequently.

**Drug Availability**

Lomitapide is available as a 5, 10, 20, 30, 40, and 60 mg capsule.

## PRECAUTIONS:

**Boxed Warning**

- Risk of hepatotoxicity, elevations in transaminases, and increases in hepatic fat; measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating and regularly as recommended
- REMS program – only certified providers may prescribe

**Contraindications**

- Pregnancy
- Concomitant administration with moderate or strong CYP3A4 inhibitors
- Moderate or severe hepatic impairment (Child-Pugh B or C)
- Active liver disease

**Precautions/Warnings**

- Reduced absorption of fat-soluble nutrients
- Risk of myopathy, including rhabdomyolysis, with simvastatin and lovastatin
- Risk of supratherapeutic or subtherapeutic anticoagulation with warfarin

## BILLING/CODING INFORMATION:

The following codes may be used to describe:

### HCPCS Coding:

| | |
|---|---|
| J8499 | Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified |

### ICD-10 Diagnosis Codes That Support Medical Necessity:

| | |
|---|---|
| E78.00 | Pure hypercholesterolemia, unspecified |
| E78.01 | Familial hypercholesterolemia |

## REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

## PROGRAM EXCEPTIONS:

**Federal Employee Program (FEP):** Follow FEP guidelines.

**State Account Organization (SAO):** Follow SAO guidelines.

**Medicare Part D:** Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

**Medicare Advantage Products:** No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

## DEFINITIONS:

None

## RELATED GUIDELINES:

**Mipomersen Sodium (Kynamro™) Injection, 09-J1000-93**

**PCSK9 Inhibitors, 09-J2000-36**

## OTHER:

**Child-Pugh Classification of Severity of Liver Disease:** Using the table below, a total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease).

### Table

| Parameter | Points assigned | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Ascites | Absent | Slight | Moderate |
| Bilirubin, mg/dL | </= 2 | 2-3 | >3 |
| Albumin, g/dL | >3.5 | 2.8-3.5 | <2.8 |

| | | | |
|---|---|---|---|
| Prothrombin time<br>* Seconds over control<br>* INR | .<br>1-3<br><1.8 | .<br>4-6<br>1.8 – 2.3 | .<br>>6<br>>2.3 |
| Encephalopathy | None | Grade 1-2 | Grade 3-4 |

## Examples of CYP3A4 Inhibitors

| Weak | Moderate | Strong |
|---|---|---|
| Alprazolam | amprenavir | boceprevir |
| amiodarone | aprepitant | clarithromycin |
| amlodipine | atazanavir | conivaptan |
| atorvastatin | ciprofloxacin | indinavir |
| bicalutamide | crizotinib | itraconazole |
| cilostazol | darunavir/ritonavir | ketoconazole |
| cimetidine | diltiazem | lopinavir/ritonavir |
| cyclosporine | erythromycin | mibefradil |
| fluoxetine | fluconazole | nefazodone |
| fluvoxamine | fosamprenavir | nelfinavir |
| ginkgo | imatinib | posaconazole |
| goldenseal | verapamil | ritonavir |
| isoniazid | | saquinavir |
| lapatinib | | telaprevir |
| nilotinib | | telithromycin |
| oral contraceptives | | voriconazole |
| pazopanib | | |
| ranitidine | | |
| ranolazine | | |
| tipranavir/ritonavir | | |
| ticagrelor | | |
| zileuton | | |

## REFERENCES:


1. Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet 2013;381(9860):40-46.
2. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. J Clin Lipidol. 2014 Sep-Oct;8(5):473-88. Epub 2014 Jul 15.
3. Juxtapid [package insert]. Cambridge, MA: Aegerion Pharmaceuticals Inc.; February 2014.
4. Lomitapide. Clinical Pharmacology [Internet Database]. Gold Standard, Inc., 2014 [cited 2014 April 22]. Available from: http://www.clinicalpharmacology-ip.com/.
5. Lomitapide. In: DRUGDEX® System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically [cited 2014 April 22]. Available from: http://www.thomsonhc.com/.
6. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners. Identification and management of familial hypercholesterolaemia (FH). 2008 [cited 2013 April 5]. Available at: www.nice.org.uk/CG71.

7. Orphan Drug Designations and Approval [Internet Database]. U.S. Food and Drug Administration, 2014 [cited 2014 April 22]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
8. Raal FJ, Santos RD. Homozygous familial hypercholesterolemia: current perspectives on diagnosis and treatment. Atherosclerosis 2012;223(2):262-268.

## COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/13/19.

## GUIDELINE UPDATE INFORMATION:

| | |
|---|---|
| 06/15/13 | New Medical Coverage Guideline. |
| 06/15/14 | Review and revision to guideline; consisting of updating references. |
| 08/15/15 | Revision to guideline; consisting of position statement. |
| 11/01/15 | Revision: ICD-9 Codes deleted. |
| 02/15/16 | Revision to guideline consisting of updating the position statement and references. |
| 10/01/16 | Revision to guideline; consisting of updating ICD10 codes |
| 01/01/20 | Updated position statement |