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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

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SUMMARY OF EVIDENCE/POSITION

This policy addresses **Juxtapid (lomitapide)** for the treatment of treatment of homozygous familial hypercholesterolemia**.** Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

- Lomitapide is approved only for **homozygous** familial hypercholesterolemia (HoFH). There is insufficient evidence from a single uncontrolled, open-label trial of 29 HoFH patients to evaluate lomitapide effectiveness to prevent CHD events. Therefore, although lomitapide demonstrated effectiveness in reducing LDL-C levels, there is uncertainty whether this equates to reduced cardiovascular morbidity and mortality.

- The current safety data does not support the use of lomitapide in patients with lower CHD risk.

- Homozygous familial hypercholesterolemia (HoFH) patients have limited therapeutic options and there is currently limited data available to be able to suggest a place in therapy for Juxtapid®. Therefore, it is recommended that Juxtapid® remain non-preferred and be available to the few who are unable to tolerate any preferred medications.

- There are no head-to-head trials comparing lomitapide to other treatments. Therefore, there is no evidence that lomitapide is safer or more effective than other treatments for homozygous familial hypercholesterolemia, including mipomersen.

- Guideline recommendations: Lomitapide may be useful in patients with HoFH not responsive to PCSK9 inhibitor therapy [AACE (Jellinger 2017)]. In addition, lomitapide may be considered in patients with ASCVD and baseline LDL-C ≥190 mg/dL who have an inadequate response to statins (with or without ezetimibe and PCSK9 inhibitors) [ACC (Lloyd-Jones 2016)].

FDA INDICATIONS

Homozygous familial hypercholesterolemia: 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 (apo B), 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 (lomitapide) have not been established in patients with hypercholesterolemia who do not have HoFH.
- The effect of Juxtapid (lomitapide) on cardiovascular morbidity and mortality has not been determined.

Available as: 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 60 mg

Approved by the FDA: December 2012

Black box warning: Hepatotoxicity. Juxtapid can cause elevations in transaminases. Juxtapid also increases hepatic fat (hepatic steatosis) with or without concomitant increases in transaminases. Juxtapid is a pregnancy category X.

REMS: Only available through the JUXTAPID REMS PROGRAM and from certified pharmacies that are enrolled in the program. Providers must be enrolled in the program in order to prescribe Juxtapid (lomitapide).

CLASSIFICATION: Antihyperlipidemic, Microsomal Triglyceride Transfer Protein (MTP) Inhibitor

Initiation of therapy with Juxtapid (lomitapide) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [BOTH]

- ❑ Board-certified clinical lipidologist (achieved certification from the American Board of Clinical Lipidology); specialist in Endocrinology, Diabetes and Metabolism; cardiologist; or hematologist
  - *According to the National Lipid Association (NLA), homozygous FH patients should always be managed by a lipid specialist.* [B]

- ❑ Prescribed by a certified REMS provider demonstrated with supporting documentation (signed attestation)

2. Diagnosis/Indication [ALL]

Documentation of diagnosis required and may include clinical notes from the member's medical records including any relevant labs and/or tests, supporting the diagnosis [ALL]

- ❑ Definitive diagnosis of **homozygous** familial hypercholesterolemia confirmed by either: [ONE]

  1) Mutations in the low-density lipoprotein receptor gene (LDLR), apolipoprotein B gene (APOB), or the pro-protein convertase subtilisin/kexin 9 gene (PCSK9); OR

  2) Cellular testing demonstrating reduced LDL receptor activity in fibroblasts / lymphocytes equaling 20% or less of the normal activity; OR

  3) A clinical diagnosis of HoFH was made based on untreated LDL-C > 500 mg/dl (> 13 mmol/L) OR treated LDL-C > 300 mg/dl (> 8 mmol/L)[Rosenson, 2020]
  AND
  Cutaneous or tendon xanthomas before age 10 OR elevated LDL-C consistent with heterozygous FH in both parents (e.g., documented history of elevated LDL-C ≥ 190 mg/dL prior to lipid-lowering therapy);

3. Age/Gender/Other restrictions [ONE]

- ❑ 18 years of age or older
  - *The safety and effectiveness of Juxtapid have not been studied in pediatric patients less than 18 years.*

- ❑ Women of childbearing age only: Negative pregnancy test within the past 30 days AND counseling for use of effective contraception during treatment and for 2 weeks after the final lomitapide dose
  - *Lomitapide may be embryotoxic; women of child-bearing potential should have a negative pregnancy test before starting treatment and use effective contraception during treatment.*

- ❑ Women who are breast feeding: Counseling on discontinuing breastfeeding due to the potential for serious adverse reactions in the breastfeeding infant.
  - *Breastfeeding is not recommended by the manufacturer.*

- ❑ Member does not have hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption
  - *Contains lactose; avoid use in patients with hereditary galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption; may result in diarrhea and malabsorption.*

4. Step/Conservative Therapy/Other condition Requirements [ALL]
Documentation of ALL of the following required and may include clinical notes from the member's medical records including any relevant labs and/or tests, supporting the diagnosis [ALL]

- ❑ Member is currently adherent to, and will continue to follow a low-fat diet supplying < 20% of energy from fat

- ❑ Member is **currently adherent to, and will continue** other standard lipid-lowering therapies including (but not limited to) the following:
  NOTE: Prescriber submit documentation of regimen, dosage and dates of therapy
  - ❍ Statin
    - *High-intensity statin therapy recommended as initial pharmacologic treatment in patients with heterozygous FH*
  - ❍ Zetia
  - ❍ LDL-C apheresis
    - *LDL cholesterol apheresis recommended in patients intolerant to conventional lipid-lowering therapy or LDL cholesterol targets not achieved on conventional lipid-lowering therapy*

- ❑ Member meets ALL the following: **[A AND B]**

A. STATINS [ONE: 1 OR 2 OR 3]

1) Inadequate clinical response (*defined as failure to reach target LDL based on individual member's goal as determined by provider) to **ONE** of the following: [ONE]
   - ❍ High-intensity statin (e.g. atorvastatin 40-80 mg daily, rosuvastatin 20-40 mg daily) for a duration of at least 8 weeks; OR
   - ❍ Maximally tolerated dose of ANY statin for a duration of at least 8 weeks due to member cannot tolerate a high-intensity statin

   ***NOTE:** Failure to reach target LDL: There is little agreement on LDL-C goal among experts; values between <50 mg/dL (1.3 mmol/L) and 135 mg/dL (3.5 mmol/L) have been noted. Values at the low end of this range may be difficult if not impossible to achieve even with multiple cholesterol-lowering agents, as well as therapies such as LDL apheresis.[Rosenson 2020]

2) Intolerance* to statins as defined by severe and intolerable adverse effects
   **e.g. Creatine kinase elevation greater than or equal to 10 times the upper limit of normal; Liver function test elevation greater than or equal to 3 times the upper limit of normal; Rhabdomyolysis, severe muscle weakness leading to temporary disability, fall, or inability to use a major muscle group)*

3) Absolute contraindication* or member has risk factor* to statin therapy

**e.g. hypersensitivity reaction; Decompensated liver disease (development of jaundice, ascites, variceal bleeding, encephalopathy); Laboratory-confirmed acute liver injury or rhabdomyolysis resulting from statin treatment; Pregnancy, planning to become pregnant, or nursing; Immune-mediated hypersensitivity to the HMG-CoA reductase inhibitor drug class (statins) as evidenced by an allergic reaction occurring with at least TWO different statins; Multiple or serious comorbidities, including impaired renal or hepatic function; Unexplained alanine aminotransferase (ALT) elevations > 3 times the upper limit of normal, or active liver disease; Concomitant use of drugs adversely affecting statin metabolism; Age > 75 years, or history of hemorrhagic stroke*

AND

B. ZETIA: Member has been on Zetia therapy adherently for at least 3 months, unless *contraindication to, or history of intolerance

**e.g., Moderate or severe hepatic impairment (Child-Pugh classes B and C), hypersensitivity (anaphylaxis, angioedema, rash, urticaria), or pregnancy*

❒ Requested therapy will be administered with the following (per labeling): daily supplements that contain 400 units of vitamin E and at least 200 mg of linoleic acid, 210 mg of alpha-linolenic acid (ALA), 110 mg of eicosapentaenoic acid (EPA), and 80 mg of docosahexaenoic acid (DHA) to reduce the risk of developing a fat-soluble nutrient deficiency

❒ Inadequate clinical response (defined as failure to reach target LDL), intolerance or contraindication to Repatha (evolocumab)

❒ Requested therapy, Juxtapid (lomitapide), will **not** be prescribed concomitantly with the following: [ALL]

- ❍ PCSK9 inhibitors [e.g., alirocumab (Praluent) and evolocumab (Repatha)]
  - *The safety and effectiveness of lomitapide have not been studied in combination with mipomersen.*
- ❍ Moderate or strong CYP3A4 inhibitors (e.g., diltiazem, fluconazole, itraconazole, ketoconazole, clarithromycin, erythromycin, HIV protease inhibitors, nefazodone)

❑ Prescriber agrees to monitoring of transaminases (ALT, AST), alkaline phosphatase, and total bilirubin prior to initiation and prior to any dose increase. Submit applicable labs with reauthorization requests.

5. **Contraindications/Exclusions to Juxtapid (lomitapide) therapy [ANY]**
   Authorization will not be granted if ANY of the following conditions apply [ANY]
   - ❑ Non-FDA approved indications
   - ❑ Hypersensitivity to Juxtapid (lomitapide) or any ingredient in the formulation
   - ❑ Pregnancy
   - ❑ Co-administration with moderate moderate (e.g. ciprofloxacin, diltiazem, fluconazole) or strong CYP3A4 inhibitors [such as boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole]
     - *CYP3A4 inhibitors increase the exposure of Juxtapid, with strong inhibitors increasing exposure approximately 27-fold.*
   - ❑ Moderate or severe hepatic impairment (Child-Pugh class B or C), active liver disease, including unexplained persistent elevations of serum transaminases

6. **Labs/Reports/Documentation required [ALL]**
   All documentation for determination of medical necessity must be submitted for review. Prescriber to submit medical records and specific labs, chart notes, and documentation as indicated in the criteria above. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP is included.
   NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

REAUTHORIZATION /CONTINUATION OF THERAPY

Continuation of therapy with Juxtapid (lomitapide) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Initial Coverage Criteria

- ❑ Member continues to meet applicable initial coverage criteria

2. Adherence to Therapy/Compliance

- ❑ Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance)
  NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

- ❑ Member continues to be adherent with the following medications in conjunction with Juxtapid (lomitapide):
  NOTE: Prescriber submit documentation of regimen, dosage and dates of therapy
  - ❍ Low fat diet
  - ❍ Other lipid-lowering therapy including:
    - Statins
    - Zetia
    - LDL-C apheresis
  - ❍ Supplement(s) that contains 400 IU vitamin E, 200 mg linoleicacid, 210 mg alpha-linoleic acid (ALA), 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA)

- ❑ Compliance to the recommended liver enzyme laboratory testing as specified in the Juxtapid prescribing information (ALT, AST, alkaline phosphatase, total bilirubin). Submit documentation of testing as it applies to member's duration of therapy
  *NOTE: Transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), alkaline phosphatase and total bilirubin should be measured prior to initial therapy and prior to each increase in dose or on a monthly basis (whichever occurs first). After the first year of treatment, testing should occur at a minimum of every three months.

3. Labs/Reports/Documentation required [ALL]

- ❑ Positive response to therapy defined as: Achieving and maintaining at least a 50% in LDL-C from baseline lowering from pre-treatment levels. Documentation required.
  NOTE: In patients at high risk for cardiovascular disease, more aggressive goals of LDL-C < 100 mg/dL and non-HDL-C < 130 mg/dL may be needed to reduce risk of cardiovascular disease.
  EXCEPTION to criteria: Submit documentation of clinical rationale addressing the appropriate reduction for member's goal if different from required criterion of 50% in LDL-C

4. Discontinuation of Treatment

- ❑ Intolerable adverse effects or drug toxicity

- ❑ Persistent or clinically significant elevations of transaminase OR if the elevations are accompanied by clinical symptoms of liver injury or toxicity, increases in bilirubin ≥ 2 times the upper limit of normal (ULN), active liver disease
- ❑ Contraindications/Exclusions to therapy [ANY]
  Authorization will not be granted if ANY of the following conditions apply [ANY]
  - ❍ Non-FDA approved indications
  - ❍ Hypersensitivity to Juxtapid (lomitapide) or any ingredient in the formulation
  - ❍ Pregnancy
  - ❍ Co-administration with moderate (i.e. ciprofloxacin, diltiazem, fluconazole) or strong CYP3A4 inhibitors [i.e. boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole]
    - *CYP3A4 inhibitors increase the exposure of Juxtapid, with strong inhibitors increasing exposure approximately 27-fold.*
  - ❍ Moderate or severe hepatic impairment (Child-Pugh class B or C), active liver disease, including unexplained persistent elevations of serum transaminases

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. **Recommended Dosing Regimen [ALL]**

- ❑ Dosage prescribed is within the FDA-approved labeling based on member's confirmed diagnosis:
  - ❍ Initial dose 5 mg orally once a day
  - ❍ Increase to 10 mg daily after at least 2 weeks based on tolerability
  - ❍ At 4 week intervals increase to 20 mg, 40mg, 60 mg (maximum dose) daily if necessary based on efficacy and tolerability

- ❑ 5 mg to 60 mg orally once daily
  - *The safety and effectiveness of higher doses have not been established.*
  - *Patients with end-stage renal disease receiving dialysis should not exceed 40 mg daily. Patients with mild hepatic impairment should not exceed 40 mg daily.*

2. **Authorization Limit [ALL]**

- ❑ Quantity limit: up to **60 mg/day [up to 90 capsules/30 days]**

- ❑ May authorize up to **6 months** of continuation of therapy

3. **Route of Administration [ALL]**

- ❑ Medication is considered to be **self-administered** until information from the manufacturer, scientific literature, practice standards, or governing State or Federal agency indicates self-administration is not safe or acceptable.

- ❒ Refer to Specialty Medication Administration Site of Care Policy P&P: MHI Pharm 11

COVERAGE EXCLUSIONS

All other uses of Lomitapide (Juxtapid) that are not an FDA-approved indication or FDA-approved indications that are not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

- ❑ **Heterozygous** familial hypercholesterolemia
  - *The safety and efficacy of Juxtapid have <u>not</u> been established in patients with hypercholesterolemia who do not have homozygous familial hypercholesterolemia.*
- ❑ Drug resistant hypercholesterolemia
- ❑ Co-administration with PCSK9 inhibitors [e.g., alirocumab (Praluent) and evolocumab (Repatha)]
- ❑ Concurrent therapy with moderate or strong CYP3A4 inhibitors (e.g., diltiazem, fluconazole, itraconazole, ketoconazole, clarithromycin, erythromycin, HIV protease inhibitors, nefazodone)

BACKGROUND/SUMMARY

Familial hypercholesterolemia (FH)

- An autosomal dominant genetic disease caused by functional mutations at one of three genetic loci: 1) low-density lipoprotein cholesterol (LDL-C) receptor, 2) apo B, or 3) proprotein convertase subtilisin kexin type 9 (PCSK9), all of which are involved in the normal processing and trafficking of LDL-C.
- In the absence of genetic testing, which confirms one of these mutations, FH is defined based on clinical criteria.
- The primary goal of treatment in patients with familial hypercholesterolemia is LDL-C lowering.

Homozygous FH (HoFH)

- Rare and is characterized by severe elevations of total and LDL cholesterol
- Leads to accumulation of LDL particles in plasma and premature cardiovascular disease.
- Patients with HoFH carry two of the same defective genes, while patients with the heterozygous form of the condition carry one defective gene. Individuals with familial hypercholesterolemia (FH) are at significantly increased risk for premature cardiovascular disease (CVD).
- Prevalent in approximately one out of a million individuals. Most patients with HoFH have LDL levels that are four times the normal levels (between 400-1,000 mg/dL).
- Patients with HoFH will form xanthelasmas (yellowish collection of cholesterol under the skin) and cutaneous xanthomas (larger, nodular xanthelasmas) within the first few months of years of life. Tendon xanthomas (papules found in tendons of hands, feet and achilles) and tuberous xanthomas (xanthomas over the joints) tend to develop in HoFH patients later on in life.
- Generally, treating patients with HoFH has been challenging because the patient expresses little or no LDL-receptor activity and therefore is resistant to diet modifications and most medications indicated for lowering cholesterol.
- Children with homozygous FH usually present within the first decade of life, most commonly after investigation of physical findings related to cholesterol deposition, such as tendon xanthomata, cutaneous xanthelasma, or corneal arcus, or with clinical manifestations of atherosclerotic cardiovascular disease. Individuals with the more severe homozygous form of FH (HoFH) develop clinically significant cardiovascular disease in early childhood and, if untreated, they rarely survive beyond the age of 30 years, whereas in those with the less severe heterozygous form (HeFH) the onset of significant cardiovascular disease is generally delayed until the fourth or fifth decade. It is noted by the American Heart Association that familial hypercholesterolemia (FH) is the most common of the primary hyperlipidemias, and the most clearly documented to have important cardiovascular consequences beginning in childhood. Hence, the identification and management of FH in children is of significant consequence.

<u>Diagnosis</u>

- No universally accepted diagnostic criteria. Formal diagnosis of FH made by applying various combinations of patient characteristics. There are 3 validated sets of diagnostic criteria include:
  - United States Make Early Diagnosis to Prevent Early Death (MedPed)
  - United Kingdom Simon Broome Familial Hypercholesterolemia Registry
  - Dutch Lipid Clinic criteria
- Diagnosis of both homozygous and heterozygous FH is based primarily on the finding of severe LDLc elevations in the absence of secondary causes of hypercholesterolemia with triglyceride levels that are within the reference range or mildly elevated and HDL cholesterol (HDLc) levels that are within the reference range or slightly low. Definitive diagnosis can be made only with gene or receptor analysis.

- HoFH can be distinguished from heterozygous FH clinically by the much more extreme elevations in LDL and can be confirmed by either genetic characterization of the LDL receptor mutations (from leukocytes) or by quantification of LDL receptor activity (from skin fibroblasts).

TREATMENT OPTIONS

The goal of FH treatment is to reduce the risk of CHD or risk of a CHD-equivalent condition (e.g., carotid artery disease, diabetes, peripheral arterial disease).

Management of homozygous FH

- Lifestyle changes: Recommended for cardiovascular benefits
- High doses of HMG-CoA reductase inhibitors (statins) combined with bile acid sequestrants, ezetimibe, and niacin
- Estrogen replacement therapy in postmenopausal women
- LDL apheresis for selective removal of lipoproteins that contain apo-B (when the LDL receptors are absent or non-functional)
- Surgical procedures: Portacaval anastomosis or Liver transplantation (rarely)

Other FDA-approved pharmacological therapies indicated for the treatment of HoFH include certain statins (atorvastatin, rosuvastatin and simvastatin), ezetimibe/simvastatin and ezetimibe in combination with either atorvastatin or simvastatin. The 2002 Adult Treatment Panel (ATP) III guidelines from the National Cholesterol Education Program (NCEP) lists statins and nicotinic acid as an adjunct to other lipid-lowering treatments such as LDL aphresis (process which removes VLDL and LDL from the plasma) or when such treatments are unavailable as therapeutic considerations in patients with HoFH.

- FH patients without cardiovascular disease who do not achieve LDL-C < 200 mg/dL (5.17 mmol/L) or those with established disease who do not achieve an LDL-C < 160 mg/dL (4.10 mmol/L) after optimal drug therapy and LDL-apheresis, we suggest adding lomitapide or mipomersen (Grade 2C). For patients who are not candidates for or refuse LDL-apheresis or liver transplantation, lomitapide or mipomersen should be considered as additional pharmacologic therapy. (UpToDate 2019)
- It should be noted that the safety and efficacy of Juxtapid (lomitapide) in children have not been established.
- American Heart Association recommendations for pediatric patients regarding homozygous familial hypercholesterolemia patients are as follows:
    - complete cardiovascular assessment at diagnosis along with ongoing surveillance for cardiovascular disease
    - treatment should be instituted as soon as possible
    - therapy for most patients is weekly or biweekly plasmapheresis, preferably LDL apheresis
    - high-dose statins recommended in combination with a cholesterol absorption inhibitor
    - low-dose anticoagulation may also be indicated

Juxtapid (lomitapide) is a first-in-class microsomal triglyceride transfer protein (MTP) inhibitor. Lomitapide is a microsomal triglyceride transfer protein inhibitor used to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol, apolipoprotein B (apo-B), and non-high-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia (HoFH). Juxtapid is intended for use in combination with a low fat diet, supplying < 20% of energy from fat, and other lipid-lowering treatments. Juxtapid directly binds and inhibits microsomal triglyceride transfer protein (MTP), which resides in the lumen of the endoplasmic reticulum, thereby preventing the assembly of apo B-containing lipoproteins in enterocytes and hepatocytes. This inhibits the synthesis of chylomicrons and VLDL. The inhibition of the synthesis of VLDL leads to reduced levels of plasma LDL-C.

Lomitapide, a synthetic lipid-lowering agent, directly binds and inhibits microsomal triglyceride transfer protein, which resides in the lumen of the endoplasmic reticulum, thereby preventing the assembly of apo B–containing lipoproteins in enterocytes and hepatocytes. This inhibits the synthesis of chylomicrons and very low-density lipoprotein (VLDL). The inhibition of the synthesis of VLDL leads to reduced levels of plasma LDL-C.

PUBLISHED CLINICAL TRIALS
To date, only one Phase III clinical trial has been published supporting lomitapide in the treatment of HoFH.

Approval was based on data from a Phase III, 78-week, single-arm, open-label trial that evaluated the use of lomitapide in 29 adult patients with homozygous familial hypercholesterolemia. Patients were treated with lomitapide at an initial dose of 5 mg daily and gradually escalated to doses of 10mg, 20mg, 40mg, up to 60mg, based on tolerability and acceptable liver enzyme levels.

The primary endpoint was LDL-C change from baseline to 26 weeks and patients were followed an additional 52 weeks to assess safety. Concomitant lipid-lowing therapies were stable during the efficacy phase but could change during the safety phase. Apheresis was allowed and LDL-C response allowed it to be stopped in 3 patients and the interval extended in another 3. There was a 50% decrease in LDL-C at 26 weeks ($p < 0.0001$) to a median level of 169 mg/dL. Eight patients achieved LDL-C levels <100mg/dL with 4 of these concomitantly receiving apheresis.

The study did not evaluate CHD events. Results from the study showed that when lomitapide was added onto existing lipid-lowering treatment, LDL cholesterol was significantly reduced from a baseline average of 336 mg/dL to 190 mg/dL (40% reduction) at week 26. In 23 patients, LDL cholesterol was reduced by an average of 50% at week 26. Among the 23 patients who completed the trial, mean LDL cholesterol decreased from a baseline of 336 mg/dL to 166 mg/dL after 26 weeks, 197 mg/dL at 56 weeks, and 208 mg/dL at 78 weeks, all significant reductions.

The most common adverse events were gastrointestinal, reported by 27 (93%) of 29 patients. Adverse events reported by ≥5% of patients with HoFH include diarrhea, nausea, vomiting, dyspepsia, abdominal pain, weight loss, abdominal discomfort, abdominal distension, constipation, flatulence, increased alanine aminotransferase, chest pain, influenza, nasopharyngitis and fatigue.

Available treatment guidelines support the use of high-dose statins, low density lipoprotein apheresis and other cholesterol lowering agents (e.g., ezetimibe), often as part of combination regimens to reach cholesterol goals.

<u>American Heart Association</u>

- The 2006 American Heart Association scientific statement on cardiovascular risk reduction in high-risk pediatric patients recommends that children with homozygous FH receive early initiation of combined therapy including LDL apheresis, high dose statin therapy, and a cholesterol absorption inhibitor. UpToDate experts on homozygous FH also recommend this approach for both children and adults.

- Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: a Scientific Statement from the American Heart Association (2007) may be given as necessary, although compliance with these agents tends to be challenging.
    - For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime.

- For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age.
- Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.

American Association of Clinical Endocrinologists (AACE 2012)

In 2012, the American Association of Clinical Endocrinologists (AACE) published guidelines for the management of dyslipidemia and prevention of atherosclerosis.

AACE also includes lipid screening in the pediatric populations and recommend that children older than two years and adolescents older than 16 years be evaluated every three to five years and every five years, respectively, if they have CAD risk factors or a family history of premature CAD or dyslipidemia.
AACE supports the use of apolipoprotein B (apo B) in evaluating lipid status. They recommend an optimal apo B < 90 mg/dL for patients at risk of CAD, while patients with established CAD or diabetes who have one or more additional risk factors should have an apo B < 80 mg/dL.

Fibrates for recommended for treatment of triglycerides > 500 mg/dL. Niacin can be used for reducing triglycerides, increasing HDL-C, and reducing LDL-C. Omega-3 fish oil (2 to 4 g) of can be used, as adjunct to fibrates or niacin if necessary, to achieve satisfactory triglyceride lowering.

AACE recommends bile acid sequestrants for reducing LDL-C and apo B and modestly increasing HDL-C, but they may increase triglycerides.

Cholesterol absorption inhibitors are effective as monotherapy in reducing LDL-C and apo B. In addition, combination therapy with statins can be used.

AACE recommends pharmacotherapy for children and adolescents older than eight years who do not respond sufficiently to lifestyle modification and particularly for those with either LDL-C ≥ 190 mg/dL, or LDL-C ≥160 mg/dL and the presence of two or more cardiovascular risk factors, or a family history of premature CAD.

These guidelines also address the unique challenges associated with atherosclerosis and heart disease in women. They recommend the following pharmacotherapy for all women at high risk: lipid-lowering pharmacotherapy (preferably with a statin) regardless of LDL-C level, and niacin or fibrate therapy in the presence of low HDL-C or elevated non–HDL-C; for all women at intermediate risk: lipid-lowering pharmacotherapy (preferably with a statin) in the presence of an LDL-C level greater than 130 mg/dL, and niacin or fibrate therapy in the presence of low HDL-C or elevated non–HDL-C after LDL-C goal is reached.

National Heart Lung and Blood Institute

Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk (2011)
Specific recommendations regarding the management of familial hypercholesterolemia include:

- Children with homozygous familial hypercholesterolemia and extremely elevated LDL-C levels (> 500 mg/dL) have undergone effective LDL-C lowering therapy with biweekly LDL apheresis under the care of lipid specialists in academic medical centers.
- Statins have been shown to reduce LDL-C in children and adolescents with marked LDL-C elevation or familial hypercholesterolemia.
- Plant sterol esters and/or plant stanol esters up to 2 g/day as replacement for usual fat sources can be used after two years of age in children with familial hypercholesterolemia

National Cholesterol Education Program (NCEP)

The 2002 Adult Treatment Panel (ATP) III guidelines from the National Cholesterol Education Program (NCEP) lists statins and nicotinic acid as an adjunct to other lipid-lowering treatments such as LDL aphresis (process which removes VLDL and LDL from the plasma) or when such treatments are unavailable as therapeutic considerations in patients with HoFH.

National Lipid Association (NLA)

Management of familial hypercholesterolemias in adult patients: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia (2011)

- Low-fat, low-cholesterol diet and tobacco cessation, physical activity and maintenance of a healthy body weight are recommended.

- For adult familial hypercholesterolemia patients, initial treatment is the use of moderate to high doses of **high-potency** statin are recommended to reduce LDL-C at least 50% from baseline. Low potency statins are generally inadequate for familial hypercholesterolemia patients. If a patient is not able to meet the LDL-C goal with statin, additional agents such as ezetimibe, bile acid sequestrants, or niacin may be added to statin therapy.

    - If the initial statin is not tolerated, consider changing to an alternative statin, or every-other-day statin therapy.

    - If initial statin therapy is contraindicated or poorly tolerated, ezetimibe, a bile acid sequestrant (colesevelam) or niacin may be considered.

    - For patients who cannot use a statin, most will require combination drug therapy.

    - If the patient is not at LDL-C treatment goal with the maximum available and tolerable dose of statin, then combine with ezetimibe, niacin, or a bile acid sequestrant (colesevelam preferred).

- Decisions regarding selection of additional drug combinations should be based on concomitant risk factors for myopathy, concomitant medications, and the presence of other disease conditions and lipid abnormalities.

- In patients who, after six months, do not have an adequate response to maximum tolerated drug therapy, LDL apheresis is indicated according to these guidelines:
    - Functional **homozygous** familial hypercholesterolemia patients with LDL-C ≥ 300 mg/dL (or non-HDL-C ≥ 330 mg/dL).
    - Functional heterozygous familial hypercholesterolemia patients with LDL-C ≥ 300 mg/dL (or non-HDL-C ≥330 mg/dL) and one or fewer risk factors.
    - Functional heterozygous familial hypercholesterolemia patients with LDL-C ≥ 200 mg/dL (or non-HDL-C ≥ 230 mg/dL) and high risk characteristics such as two or more risk factors or high lipoprotein (a) ≥50 mg/dL using an isoform insensitive assay.
    - Functional heterozygotes with LDL-C ≥ 160 mg/dL (or non-HDL-C ≥ 190 mg/dL) and very high-risk characteristics (established CHD, other cardiovascular disease, or diabetes).

  LDL-C apheresis is recommended for patients with HoFH who have an LDL-C level of at least 300 mg/dL despite maximal drug therapy for at least six months.

- Liver transplantation is rarely utilized due to its risks, but it may be beneficial in patients who fail to respond to all other therapies because it provides normal LDL-C receptors and often leads to a significant lowering of LDL cholesterol.

Definitions

N/A

Appendix

FDA-approved lipid lowering medications or pharmaceutical agents

Generic Name	U.S. Trade Name	Route	Class
Abbreviations: FDA = U.S. Food and Drug Administration; HMG-CoA = 3-hydroxy-3-methyl-glutaryl- coenzyme A reductase; N/A = not applicable; XL = extended release			
Atorvastatin	Lipitor®	Oral	HMG-CoA reductase inhibitor (statin)
Fluvastatin	Lescol®	Oral	HMG-CoA reductase inhibitor (statin)
Fluvastatin XL	Lescol XL®	Oral	HMG-CoA reductase inhibitor (statin)
Lovastatin	Mevacor®	Oral	HMG-CoA reductase inhibitor (statin)
Pitavastatin	Livalo®	Oral	HMG-CoA reductase inhibitor (statin)
Pravastatin	Pravachol®	Oral	HMG-CoA reductase inhibitor (statin)
Rosuvastatin	Crestor®	Oral	HMG-CoA reductase inhibitor (statin)
Simvastatin	Zocor®	Oral	HMG-CoA reductase inhibitor (statin)
Cholestyramine	Prevalite®	Oral	Bile acid sequestrant
Colesevelam	Welchol®	Oral	Bile acid sequestrant
Colestipol	Colestid®; Flavored Colestid®	Oral	Bile acid sequestrant
Ezetimibe	Zetia®	Oral	Cholesterol absorption inhibitor
Fenofibrate	Tricor®; Triglide®; Lipofen®; Fenoglide®	Oral	Fibric acid
Fenofibric acid	Fibricor®; Trilipix®	Oral	Fibric acid
Gemfibrozil	Lopid®	Oral	Fibric acid
Niacin	Niaspan®; Niacor®	Oral	Nicotinic acid
Omega-3-acid ethyl ester	Lovaza®; Omacor®	Oral	Omega-3-acid ethyl ester
Icosapent ethyl	Vascepa®	Oral	Omega-3-acid ethyl ester
Lovastatin + niacin	Advicor®	Oral	HMG-CoA reductase inhibitor (statin) + nicotinic acid

FDA-approved lipid lowering medications or pharmaceutical agents			
Generic Name	**U.S. Trade Name**	**Route**	**Class**
Simvastatin + ezetimibe	Vytorin®	Oral	HMG-CoA reductase inhibitor (statin) + ezetimibe
Simvastatin + niacin	Simcor®	Oral	HMG-CoA reductase inhibitor (statin) + nicotinic acid

Reference: Agency for Health Research and Quality (AHRQ) Effective Healthcare Program. Update of Comparative Effectiveness of Lipid-Modifying Agents. Published online: May 16, 2013. Available at: www.effectivehealthcare.ahrq.gov

CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

CPT	Description

HCPCS	Description
J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

**CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).*

REFERENCES

Package Insert and FDA

Juxtapid (lomitapide) [prescribing information]. Cambridge, MA: Aegerion Pharmaceuticals Inc; December 2019..

Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. Available at www.clinicalpharmacology.com. Accessed May 2020. [via subscription]

Drug Facts and Comparisons. Facts and Comparisons eAnswers [online]. Clinical Drug Information LLC, 2020. Available from Wolters Kluwer Health, Inc. Accessed May 2020. [via subscription]

Clinical Trials, Definitions

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.

FDA. Lomitapide Summary Review. Reference ID 3236195. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203858Orig1s000SumR.pdf. Accessed September 2013.

Ueda M. Familial hypercholesterolemia. Mol Genet Metab. Dec 2005;86(4):423-6.

Marks D, Thorogood M, Neil HA, Humphries SE. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis. May 2003;168(1):1-14.

DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. *T115368*, *Familial Hypercholesterolemia*; [updated *2018 Nov 30*, cited May 2020]. Available from https://www.dynamed.com/topics/dmp~AN~*T115368*. Registration and login required.

Peer-Reviewed Publications

The Medical Letter on Drugs and Therapeutics. Lipid-Lowering Drugs, Med Lett Drugs Ther. 2019 Feb 11;61(1565):17-24. Accessed May 2020. [via subscription]

Rosenson, RS. Treatment of drug-resistant hypercholesterolemia. In: **UpToDate [Internet Database].** Freeman, MW ed. Waltham, MA: UpToDate. Updated Jul 25, 2018. Accessed on May 2020 [via subscription]

Rosenson, RS. Familial hypercholesterolemia in adults: Treatment. In: **UpToDate [Internet Database].** Freeman, MW ed. Waltham, MA: UpToDate. Updated Nov 13, 2019. Accessed on May 2020 [via subscription]

Government Agencies, Professional Societies, and Other Authoritative Publications

National Lipid Association (NLA) expert panel on familial hypercholesterolemia

- Clinical guideline on familial hypercholesterolemia: screening, diagnosis, and management of pediatric and adult patients can be found in J Clin Lipidol 2011 Jun;5(3 Suppl):S1
- Recommendations on treatment of adults with familial hypercholesterolemia and evidence for treatment can be found in J Clin Lipidol 2011 Jun;5(3 Suppl):S18
- Recommendations on pediatric aspects of familial hypercholesterolemias can be found in J Clin Lipidol 2011 Jun;5(3 Suppl):S30
- Recommendations on management of familial hypercholesterolemias in adult patients can be found in J Clin Lipidol 2011 Jun;5(3 Suppl):S38

National Institute for Health and Clinical Excellence. Identification and management of familial hypercholesterolemia. Clinical Policy 71 2008. London: NICE 2008. Available at: http://policy.nice.org.uk/CG71/Policy/pdf/English. Accessed September 2013

National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002; 106:3143–3421. Available at: http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm. Accessed September 2013.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of **The National Cholesterol Education Program (NCEP) Expert Panel** on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. May 16 2001;285(19):2486-97.

Raal, Frederick et al. Elevated PCSK9 Levels in Untreated Patients With Heterozygous or Homozygous Familial Hypercholesterolemia and the Response to High-Dose Statin Therapy. Journal of **American Heart Association**. 2013; Apr 24, 2013; 2:28-28. doi: 10.1161/JAHA.112.000028

Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; **National Heart, Lung, and Blood Institute.** Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011 Dec;128 Suppl 5:S213-56.

American College of Cardiology (ACC)

- ACC scientific expert panel consensus on clinical genetic testing for familial hypercholesterolemia can be found in J Am Coll Cardiol 2018 Aug 7;72(6):662
- ACC 2017 focused update on role of non-statin therapies for LDL-cholesterol lowering in management of atherosclerotic cardiovascular disease risk can be found in J Am Coll Cardiol 2017 Oct 3;70(14):1785 full-text

American Association of Clinical Endocrinologists/American College of Endocrinologists (AACE/ACE) Guideline on management of dyslipidemia and prevention of cardiovascular disease can be found in Endocr Pract 2017 Apr;23(Suppl 2):1

American College of Cardiology/American Heart Association (ACC/AHA) Guideline on management of blood cholesterol can be found in J Am Coll Cardiol 2018 Nov 8:S0735

2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2016;68(1):92-125.[PubMed 27046161]

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:e285–350.
Stone NJ, Robinson JG, Lichtenstein AH, et al. **2013 ACC/AHA guideline** on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 129:S1.

Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. **A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society.** Eur Heart J 2014; 35:2146.

Policy History	Approval
Policy Developed AMR Peer Review Network. Practicing Physician. Board certified in Internal Medicine, Endocrinology, Diabetes and Metabolism. Date completed: 9/23/2013.	MCPC 10/30/2013
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Revision* AMR Peer Review Network. Practicing Physician. Board certified in Endocrinology, Diabetes and Metabolism. Date completed: 10/11/2019	P&T Q4 2019
Revision* AMR Peer Review Network. Practicing Physician. Board certified in Internal Medicine, Endocrinology (Diabetes and Metabolism). Date completed: 5/29/2020 Notable updates:	P&T Q3 2020

• Removed criteria and references to Kynamro (no longer on the market) • Revised one criterion under clinical diagnosis of HoFH ***from*** "Adult: Cholesterol above 7.5mmol/l or LDL cholesterol above 4.9 mmol/l, or Child under 16: Cholesterol above 6.7mmol/l or LDL cholesterol above 4 mmol/l" ***to*** "based on untreated LDL-C > 500 mg/dl (> 13 mmol/L) OR treated LDL-C > 300 mg/dl (> 8 mmol/L)" • Modification to criteria for women of childbearing age to include 'counseling for use of effective contraception during treatment and for 2 weeks after the final lomitapide dose' • Added criterion: 'Women who are breast feeding' • Added criterion: Member does not have hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption • Added criteria for Zetia: 'Member has been on Zetia therapy adherently for at least 3 months, unless *contraindication to, or history of intolerance' • Added adherence criterion to recommended regimen to 'Continuation of therapy' section: 'Member continues to be adherent with the following medications in conjunction with Juxtapid (lomitapide)' • Modification of Continuation therapy criterion ***from*** 'Demonstrated efficacy by significant LDL lowering from pre-treatment levels. Documentation required' ***to*** 'Positive response to therapy defined as achieving and maintaining at least a 50% in LDL-C from baseline' • Updated 'Exclusions' section to include 'Co-administration with PCSK9 inhibitors [e.g., alirocumab (Praluent) and evolocumab (Repatha)]' and 'Concurrent therapy with moderate or strong CYP3A4 inhibitors (e.g., diltiazem, fluconazole, itraconazole, ketoconazole, clarithromycin, erythromycin, HIV protease inhibitors, nefazodone)'	

*NOTE: All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence for both 'Annual Reviews' and 'Revisions.' Revisions include notable content updates or revisions that which may have affected criteria or requires review by a practicing specialist, Peer Reviewer. The revisions noted below but may not be all-inclusive of all revised criteria and content in each policy; refer to MCP for all revisions and complete context.