Drug Monograph

Drug/Drug Class:	**Juxtapid™ (lomitapide mesylate) Capsule / triglyceride transfer protein inhibitor**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Juxtapid™ is available in 5mg, 10mg and 20mg strength capsules containing 5mg, 10mg and 20mg respectively of lomitapide mesylate. Aegerion Pharmaceuticals, Inc. Cambridge, MA 02142
Summary of Findings:	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, total cholesterol, apolipoprotein B and non-high-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia (HoFH).
Status Recommendation:	☒ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☐ PDL Product
Type of PA Criteria:	☐ Increased Risk of ADE ☐ No PA Required ☒ Appropriate Indications ☐ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

HoFH is a rare inherited condition that makes the body unable to remove LDL cholesterol, causing abnormally high levels of circulating LDL cholesterol. 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.

Dosage Form(s) [1]

Juxtapid™ is available in 5mg, 10mg and 20mg strength capsules containing 5mg, 10mg and 20mg respectively of lomitapide mesylate.

Manufacturer

Aegerion Pharmaceuticals, Inc. Cambridge, MA 02142

Indication(s) [1]

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, total cholesterol, apolipoprotein B and non-high-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia (HoFH).

Clinical Efficacy[1-7] (mechanism of action/pharmacology, comparative efficacy)

PHARMACOLOGY (1-3)

Juxtapid™ directly binds and inhibits microsomal triglyceride transfer protein (MTP), which resides in the lumen of the endoplasmic reticulum, thereby preventing the assembly of apolipoprotein 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.

PHARMACOKINETICS (1)

Juxtapid™ is 99.8% protein bound with a volume of distribution of 985-1292 L. It is metabolized by the liver and excreted in both urine and feces with a half-life of 39.7 hours.

EFFICACY (1,3-7)

SUMMARY

The approval of Juxtapid™ was primarily based upon a multinational, single-arm, open-label, 78-week clinical trial involving 29 adults with HoFH. Study results indicated that at week 26, the mean and median percent changes in LDL-C from baseline were -40% and -50%, respectively.

CONCLUSION (1,4)

Juxtapid™ is effective as an adjunctive treatment for adult patients with homozygous familial hypercholesterolemia (HoFH).

HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

STUDY DESIGN	Multinational, single-arm, open-label, 78-week clinical trial (n=29).
INCLUSION CRITERIA	Patients aged 18 years or older with HoFH. A diagnosis of HoFH was defined by the presence of at least one of the following clinical criteria: (1) documented functional mutation(s) in both LDL receptor alleles or alleles known to affect LDL receptor functionality, (2) skin fibroblast LDL receptor activity < 20% normal, or (3) untreated TC > 500 mg/dL and triglycerides < 300 mg/dL and both parents with documented untreated TC > 250 mg/dL. Among the 29 patients enrolled, the mean age was 30.7 years (range, 18 to 55 years), 16 (55%) were men, and the majority (86%) were Caucasian. The mean body mass index (BMI) was 25.8 kg/m(2), with 4 patients meeting BMI criteria for obesity; one patient had type 2 diabetes. Concomitant lipid-lowering treatment at baseline included one or more of the following: statin (93%), ezetimibe (76%), nicotinic acid (10%), bile acid sequestrant (3%), and fibrate (3%); 18 (62%) patients were receiving apheresis.
EXCLUSION CRITERIA	Major surgery in the previous 3 months, congestive heart failure, history of liver disease or hepatic transaminases greater than twice the ULN, serum creatinine > 221 mcmol/L, recent malignancy, alcohol or drug abuse, known bowel disease or malabsorption, or chronic lung disease.
TREATMENT REGIMEN	After a 6-week run-in period to stabilize lipid-lowering treatments, including the establishment of an LDL apheresis schedule if applicable, oral Juxtapid™ was initiated as 5 mg/day 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 hepatic transaminases. Patients were instructed to maintain a low-fat diet (< 20% calories from fat) and to take dietary supplements that included vitamin E 400 international units/day, alpha-linolenic acid 210 mg/day, linoleic acid 200 mg/day, eicosapentaenoic acid 110 mg/day, and docosahexaenoic acid 80 mg/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 the 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.
RESULTS	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.
SAFETY	The most common adverse reactions were diarrhea, nausea, vomiting, dyspepsia, and abdominal pain.

Contraindications[1]

- Pregnancy.
- Concomitant use with strong or moderate CYP3A4 inhibitors.
- Moderate or severe hepatic impairment or active liver disease including unexplained persistent abnormal liver function tests.

Warnings and Precautions[1]

- Embryofetal toxicity is possible; negative pregnancy tests are required prior to initiation; pregnancy should be avoided during therapy.
- Gastrointestinal adverse reactions (eg, diarrhea, vomiting, abdominal pain or distension) may be severe and could affect absorption of concomitant oral medications; a low-fat diet and dose titration may minimize adverse effects.
- Hepatic transaminase elevations and hepatic steatosis are possible; monitor and reduce dose or discontinue if necessary; availability is restricted based on REMS program guidelines.
- Fat-soluble nutrient absorption may be decreased, especially with chronic bowel or pancreatic diseases; daily nutrient supplements are recommended during therapy.
- Hereditary disorders of galactose intolerance, Lapp lactase deficiency, or glucose- galactose malabsorption may cause diarrhea and malabsorption issues; avoid use in patients with these conditions.

Adverse Effects[1]

Most common, >= 10%	**JUXTAPID™**
▪ Diarrhea	79%
▪ Nausea	65%
▪ Dyspepsia	38%
▪ Abdominal pain	34%
▪ Vomiting	34%
▪ Chest pain	24%

▪ Decreased weight	24%
▪ Abdominal discomfort	21%
▪ Abdominal distension	21%
▪ Constipation	21%
▪ Flatulence	21%
▪ Influenza	21%

▪ Fatigue	17%
▪ Increased ALT	17%
▪ Nasopharyngitis	17%
▪ Back pain	14%
▪ Gastroenteritis	14%
▪ Pharyngolaryngeal pain	14%
▪ Angina pectoris	10%
▪ Defecation urgency	10%

▪ Dizziness	10%
▪ Fever	10%
▪ Gastroesophageal reflux disease	10%
▪ Headache	10%
▪ Nasal congestion	10%
▪ Palpitations	10%
▪ Rectal tenesmus	10%

Drug Interactions[1]

- Bile acid sequestrants
- CYP3A4 inhibitors
- Lovastatin
- P-g Bile acid sequestrants
- CYP3A4 inhibitors
- Lovastatin
- P-glycoprotein substrates
- Simvastatin
- Warfarin
- lycoprotein substrates
- Simvastatin
- Warfarin

Dosage and Administration[1]

Initiate treatment at 5 mg orally once daily. Titrate dose based on acceptable safety/tolerability to 10 mg daily after at least 2 weeks, then at a minimum of 4-week intervals to 20 mg, 40 mg, and 60 mg daily (maximum recommended dose). The capsules should be taken whole, with water, and without food (at least 2 hours after evening meal). Dose modifications are necessary for patients with elevated transaminases, renal impairment, or hepatic impairment, and concomitant use of CYP3A4 inhibitors.

Cost Comparisons (at commonly used dosages)

COST *

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ MONTH
Lomitapide	Juxtapid	Aegerion	5 mg capsules	1 capsule daily	$ 27,362.10
			10 mg capsules	1 capsule daily	$ 27,362.10
			20 mg capsules	1 capsule daily	$ 27,362.10

*Missouri Maximum Allowable Cost (MO MAC)

Conclusion

Juxtapid™ is a microsomal triglyceride transfer protein inhibitor that has demonstrated efficacy as an adjunctive treatment option for adult patients with homozygous familial hypercholesterolemia. HoFH is a rare inherited condition that makes the body unable to remove LDL cholesterol, causing abnormally high levels of circulating LDL cholesterol. 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. The US Food and Drug Administration (FDA) approved Juxtapid™ with a Risk Evaluation and Mitigation Strategy (REMS) that consists of

elements to ensure safe use, including prescriber and pharmacy certification and documentation of a prescription authorization form that will accompany each new prescription. The FDA is requiring 3 postmarketing studies for Juxtapid™: 1) an animal study to evaluate the potential for toxicity in children and teens, 2) a long-term registry of patients with HoFH treated with lomitapide to determine long-term safety, and 3) an enhanced pharmacovigilance program to monitor reports of malignancy, teratogenicity, and hepatic abnormalities. The FDA designated lomitapide as an orphan drug.

Recommendation

The MO HealthNet Division recommends prior authorization status for this product.

References

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3. Stefanutti C, Morozzi C & Di Giacomo: New clinical perspectives of hypolipidemic drug therapy in severe hypercholesterolemia. Curr Med Chem 2012; 19(28):4861-4868.
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7. Rizzo M: Lomitapide, a microsomal triglyceride transfer protein inhibitor for the treatment of hypercholesterolemia. IDrugs 2010; 13(2):103-111.

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