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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use JUXTAPID safely and effectively. See full prescribing information for JUXTAPID.

JUXTAPID™ (lomitapide) capsules, for oral use
Initial U.S. Approval: 2012

WARNING: RISK OF HEPATOTOXICITY
See full prescribing information for complete boxed warning.

JUXTAPID can cause elevations in transaminases (5.1).

- **Measure alanine and aspartate aminotransferases (ALT, AST), alkaline phosphatase, and total bilirubin before initiating treatment and then ALT and AST regularly as recommended (2.4, 5.1).**
- **During treatment, adjust the dose of JUXTAPID if the ALT or AST is ≥3 times the upper limit of normal (ULN) (2.4, 5.1).**
- **Discontinue JUXTAPID for clinically significant liver toxicity (2.4, 5.1).**

JUXTAPID increases hepatic fat (hepatic steatosis) with or without concomitant increases in transaminases (5.1).

- **Hepatic steatosis associated with JUXTAPID may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis (5.1).**

Because of the risk of hepatotoxicity, JUXTAPID is available only through a restricted program called the JUXTAPID REMS PROGRAM (5.2).

INDICATIONS AND USAGE

JUXTAPID is a microsomal triglyceride transfer protein inhibitor indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH) (1).

Limitations of Use

- The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH (1).
- The effect of JUXTAPID on cardiovascular morbidity and mortality has not been determined (1).

DOSAGE AND ADMINISTRATION

- Before treatment, measure ALT, AST, alkaline phosphatase, and total bilirubin; obtain a negative pregnancy test in females of reproductive potential; and initiate a low-fat diet supplying <20% of energy from fat (2.1).
- Initiate treatment at 5 mg once daily. Titrate dose based on acceptable safety/tolerability: increase to 10 mg daily after at least 2 weeks; and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and up to the maximum recommended dose of 60 mg daily (2.1).
- Due to reduced absorption of fat-soluble vitamins/fatty acids: Take daily vitamin E, linoleic acid, alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) supplements (2.1, 5.4)
- Take once daily, whole, with water and without food, at least 2 hours after evening meal (2.2).
- Patients with end-stage renal disease on dialysis or with baseline mild hepatic impairment should not exceed 40 mg daily (2.5, 2.6).

DOSAGE FORMS AND STRENGTHS

Capsules: 5 mg, 10 mg, and 20 mg (3).

CONTRAINDICATIONS

- Pregnancy (4)
- Concomitant use with strong or moderate CYP3A4 inhibitors (4).
- Moderate or severe hepatic impairment or active liver disease including unexplained persistent abnormal liver function tests (4).

WARNINGS AND PRECAUTIONS

- Embryo-Fetal Toxicity: Females of Reproductive Potential should have a negative pregnancy test before starting JUXTAPID and use contraception during treatment (5.3)
- Gastrointestinal adverse reactions occur in 93% of patients and could affect absorption of concomitant oral medications (5.5).

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥28%) are diarrhea, nausea, vomiting, dyspepsia, and abdominal pain (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Aegerion Pharmaceuticals at 1-855-303-2347 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP3A4 inhibitors increase exposure to lomitapide. Strong and moderate CYP3A4 inhibitors are contraindicated with JUXTAPID. Patients must avoid grapefruit juice. Do not exceed 30 mg daily of JUXTAPID when used concomitantly with weak CYP3A4 inhibitors, including atorvastatin and oral contraceptives (2.3, 4, 5.6, 7.1, 7.2).
- Warfarin: Lomitapide increases plasma concentrations of warfarin. Monitor international normalized ratio (INR) regularly, especially with JUXTAPID dose adjustment (5.8, 7.3).
- Simvastatin and lovastatin exposure increase with JUXTAPID. Limit dose when co-administered with JUXTAPID due to myopathy risk (5.7, 7.4).
- P-glycoprotein (P-gp) Substrates: Consider dose reduction of P-gp substrate because of possible increased absorption with JUXTAPID (7.5).
- Bile Acid Sequestrants: Separate JUXTAPID dosing by at least 4 hours (7.6).

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Discontinue drug or nursing (8.3).
- Pediatric Patients: Safety and effectiveness not established (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2012

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF HEPATOTOXICITY

JUXTAPID can cause elevations in transaminases. In the JUXTAPID clinical trial, 10 (34%) of the 29 patients treated with JUXTAPID had at least one elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3x upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR), or alkaline phosphatase *[see Warnings and Precautions (5.1)]*.

JUXTAPID also increases hepatic fat, with or without concomitant increases in transaminases. The median absolute increase in hepatic fat was 6% after both 26 and 78 weeks of treatment, from 1% at baseline, measured by magnetic resonance spectroscopy. Hepatic steatosis associated with JUXTAPID treatment may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis *[see Warnings and Precautions (5.1)]*.

Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then ALT and AST regularly as recommended. During treatment, adjust the dose of JUXTAPID if the ALT or AST are ≥3x ULN. Discontinue JUXTAPID for clinically significant liver toxicity [*see Dosage and Administration (2.4)* and *Warnings and Precautions (5.1)*].

Because of the risk of hepatotoxicity, JUXTAPID is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the JUXTAPID REMS PROGRAM *[see Warnings and Precautions (5.2)]*.

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1. INDICATIONS AND USAGE

1.1 Homozygous Familial Hypercholesterolemia

JUXTAPID is indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (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 have not been established in patients with hypercholesterolemia who do not have HoFH.
- The effect of JUXTAPID on cardiovascular morbidity and mortality has not been determined.

2 DOSAGE AND ADMINISTRATION

2.1 Initiation and Maintenance of Therapy

Before beginning treatment with JUXTAPID:

- Measure transaminases (ALT, AST), alkaline phosphatase, and total bilirubin *[see Warnings and Precautions (5.1)]*;
- Obtain a negative pregnancy test in females of reproductive potential *[see Warnings and Precautions (5.3)]*; and,
- Initiate a low-fat diet supplying <20% of energy from fat *[see Warnings and Precautions (5.5)]*.

The recommended starting dosage of JUXTAPID is 5 mg once daily, and the dose should be escalated gradually based on acceptable safety and tolerability. Transaminases should be measured prior to any increase in dose *[see Warnings and Precautions (5.1)]*. The maintenance dosage of JUXTAPID should be individualized, taking into account patient characteristics such as goal of therapy and response to treatment, to a maximum of 60 mg daily as described in Table 1. Modify dosing for patients taking concomitant CYP3A4 inhibitors, renal impairment, or baseline hepatic impairment *[see Dosing and Administration (2.3), (2.5), and (2.6)]*. Dose adjustments are also required for patients who develop transaminase values ≥3x the upper limit of normal (ULN) during treatment with JUXTAPID *[see Dosage and Administration (2.4)]*.

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Table 1: Recommended Regimen for Titrating Dosage

DOSAGE	DURATION OF ADMINISTRATION BEFORE CONSIDERING INCREASE TO NEXT DOSAGE
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 dosage

To reduce the risk of developing a fat-soluble nutrient deficiency due to JUXTAPID's mechanism of action in the small intestine, patients treated with JUXTAPID should take daily supplements that contain 400 international units vitamin E and at least 200 mg linoleic acid, 210 mg alpha-linolenic acid (ALA), 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA) *[see Warnings and Precautions (5.4)]*.

2.2 Administration

JUXTAPID should be taken once daily with a glass of water, without food, at least 2 hours after the evening meal because administration with food may increase the risk of gastrointestinal adverse reactions *[see Warnings and Precautions (5.5)]*. Patients should swallow JUXTAPID capsules whole. Capsules should not be opened, crushed, dissolved, or chewed.

2.3 Dosing with Cytochrome P450 3A4 Inhibitors

JUXTAPID is contraindicated with concomitant use of moderate and strong cytochrome P450 3A4 (CYP3A4) inhibitors *[see Contraindications (4) and Drug Interactions (7.1)]*.

The recommended maximum dosage of JUXTAPID is 30 mg daily with concomitant use of weak CYP3A4 inhibitors (such as alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, lapatinib, nilotinib, oral contraceptives, pazopanib, ranitidine, ranolazine, tipranavir/ritonavir, ticagrelor, zileuton) *[see Drug Interactions (7.2)]*.

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2.4 Dose Modification Based on Elevated Transaminases

Table 2 summarizes recommendations for dose adjustment and monitoring for patients who develop elevated transaminases during therapy with JUXTAPID *[see Warnings and Precautions (5.1)]*.

Table 2: Dose Adjustment and Monitoring for Patients with Elevated Transaminases

ALT OR AST	TREATMENT AND MONITORING RECOMMENDATIONS*
≥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. In these cases of persistent or worsening abnormalities, also investigate to identify the probable cause. • If resuming JUXTAPID after transaminases resolve to <3x ULN, consider reducing the dose and monitor liver-related tests more frequently.
≥5x ULN	• Withhold dosing, obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR), and investigate to identify the probable cause. • If resuming JUXTAPID after transaminases resolve to <3x ULN, reduce the dose and monitor liver-related tests more frequently.

*Recommendations based on an ULN of approximately 30-40 international units/L.

If transaminase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms), increases in bilirubin ≥2x ULN, or active liver disease, discontinue treatment with JUXTAPID and investigate to identify the probable cause *[see Warnings and Precautions (5.1)]*.

2.5 Dosing in Patients with Renal Impairment

Patients with end-stage renal disease receiving dialysis should not exceed 40 mg daily. There are no data available to guide dosing in other patients with renal impairment *[see Use in Specific Populations (8.7)]*.

2.6 Dosing in Patients with Baseline Hepatic Impairment

Patients with mild hepatic impairment (Child-Pugh A) should not exceed 40 mg daily *[see Use in Specific Populations (8.8)]*.

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3 DOSAGE FORMS AND STRENGTHS

5 mg: Orange/orange hard gelatin capsule printed with black ink “A733” and “5 mg”
10 mg: Orange/white hard gelatin capsule printed with black ink “A733” and “10 mg”
20 mg: White/white hard gelatin capsule printed with black ink “A733” and “20 mg”

4 CONTRAINDICATIONS

JUXTAPID is contraindicated in the following conditions:

- Pregnancy *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)]*.
- Concomitant administration of JUXTAPID with moderate or strong CYP3A4 inhibitors, as this can increase JUXTAPID exposure *[see Warnings and Precautions (5.6), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*.
- Patients with moderate or severe hepatic impairment (based on Child-Pugh category B or C) and patients with active liver disease, including unexplained persistent elevations of serum transaminases *[see Warnings and Precautions (5.1) and Use in Special Populations (8.8)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Hepatotoxicity

JUXTAPID can cause elevations in transaminases and hepatic steatosis, as described below *[see Warnings and Precautions (5.2)]*. To what extent JUXTAPID-associated hepatic steatosis promotes the elevations in transaminases is unknown. Although cases of hepatic dysfunction (elevated transaminases with increase in bilirubin or INR) or hepatic failure have not been reported, there is concern that JUXTAPID could induce steatohepatitis, which can progress to cirrhosis over several years. The clinical studies supporting the safety and efficacy of JUXTAPID in HoFH would have been unlikely to detect this adverse outcome given their size and duration *[see Clinical Studies (14)]*.

Elevation of Transaminases

Elevations in transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) are associated with JUXTAPID. In the clinical trial, 10 (34%) of the 29 patients with HoFH had at least one elevation in ALT or AST ≥3x ULN, and 4 (14%) of the patients had at least one elevation in ALT or AST ≥5x ULN. There were no concomitant or subsequent clinically meaningful elevations in bilirubin, INR, or alkaline phosphatase *[see Adverse Reactions (6.1)]*.

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During the 78-week HoFH clinical trial, no patients discontinued prematurely because of elevated transaminases. Among the 19 patients who subsequently enrolled in the HoFH extension study, one discontinued because of increased transaminases that persisted despite several dose reductions, and one temporarily discontinued because of markedly elevated transaminases (ALT 24x ULN, AST 13x ULN) that had several possible causes, including a drug-drug interaction between JUXTAPID and the strong CYP3A4 inhibitor clarithromycin *[see Drug Interactions (7.1)]*.

Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiation of treatment with JUXTAPID *[see Dosage and Administration (2.1)]*. JUXTAPID is contraindicated in patients with moderate or severe hepatic impairment, or active liver disease, including unexplained persistent elevations of serum transaminases. If the baseline liver-related tests are abnormal, one may consider initiating JUXTAPID after an appropriate work-up and the baseline abnormalities are explained or resolved. During the first year, measure liver-related tests (ALT and AST, at a minimum) prior to each increase in dose or monthly, whichever occurs first. After the first year, do these tests at least every 3 months and before any increase in dose. Modify the dose of JUXTAPID if elevations of transaminases are observed and discontinue JUXTAPID for persistent or clinically significant elevations *[see Dosage and Administration (2.4)]*.

If transaminase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms), increases in bilirubin ≥2x ULN, or active liver disease, discontinue treatment with JUXTAPID and identify the probable cause.

Hepatic Steatosis

JUXTAPID increases hepatic fat, with or without concomitant increases in transaminases. Hepatic steatosis is a risk factor for progressive liver disease, including steatohepatitis and cirrhosis. The long-term consequences of hepatic steatosis associated with JUXTAPID treatment are unknown. During the HoFH clinical trial, the median absolute increase in hepatic fat was 6% after both 26 weeks and 78 weeks of treatment, from 1% at baseline, measured by magnetic resonance spectroscopy (MRS) *[see Adverse Reactions (6.1)]*. Clinical data suggest that hepatic fat accumulation is reversible after stopping treatment with JUXTAPID, but whether histological sequelae remain is unknown, especially after long-term use; protocol liver biopsies were not performed in the HoFH clinical trial.

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Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. It is recommended that patients taking JUXTAPID should not consume more than one alcoholic drink per day.

Caution should be exercised when JUXTAPID is used with other medications known to have potential for hepatotoxicity, such as isotretinoin, amiodarone, acetaminophen (>4 g/day for ≥3 days/week), methotrexate, tetracyclines, and tamoxifen. The effect of concomitant administration of JUXTAPID with other hepatotoxic medications is unknown. More frequent monitoring of liver-related tests may be warranted.

5.2 JUXTAPID REMS PROGRAM

Because of the risk of hepatotoxicity associated with JUXTAPID therapy, JUXTAPID is available through a restricted program under the REMS. Under the JUXTAPID REMS, only certified healthcare providers and pharmacies may prescribe and distribute JUXTAPID. Further information is available at www.JUXTAPIDREMSProgram.com or by telephone at 1-85-JUXTAPID (1-855-898-2743).

5.3 Embryo-Fetal Toxicity

JUXTAPID may cause fetal harm when administered to a pregnant woman based on findings of teratogenicity in rats and ferrets *[see Use in Specific Populations (8.1)]*. Females of reproductive potential should have a negative pregnancy test before starting JUXTAPID and should use effective contraception during therapy with JUXTAPID *[see Use in Specific Populations (8.6)]*. If oral contraceptives are used, the maximum recommended dosage of JUXTAPID is 30 mg daily *[see Dosage and Administration (2.3) and Drug Interactions (7.2)]*.

5.4 Reduced Absorption of Fat-Soluble Vitamins and Serum Fatty Acids

Given its mechanism of action in the small intestine, JUXTAPID may reduce the absorption of fat-soluble nutrients. In the HoFH clinical trial, patients were provided daily dietary supplements of vitamin E, linoleic acid, alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). In this trial, the median levels of serum vitamin E, ALA, linoleic acid, EPA, DHA, and arachidonic acid decreased from baseline to Week 26 but remained above the lower limit of the reference range. Adverse clinical consequences of these reductions were not observed with JUXTAPID treatment of up to 78 weeks. Patients treated with JUXTAPID should take daily supplements that contain 400 international units vitamin E and at least 200 mg linoleic acid, 210 mg ALA, 110 mg EPA, and 80 mg DHA *[see Dosage and Administration*

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(2.1)]. Patients with chronic bowel or pancreatic diseases that predispose to malabsorption may be at increased risk for deficiencies in these nutrients with use of JUXTAPID.

5.5 Gastrointestinal Adverse Reactions

Gastrointestinal adverse reactions were reported by 27 (93%) of 29 patients in the HoFH clinical trial. Diarrhea occurred in 79% of patients, nausea in 65%, dyspepsia in 38%, and vomiting in 34%. Other reactions reported by at least 20% of patients include abdominal pain, abdominal discomfort, abdominal distension, constipation, and flatulence *[see Adverse Reactions (6)]*.

Gastrointestinal adverse reactions of severe intensity were reported by 6 (21%) of 29 patients in the HoFH clinical trial, with the most common being diarrhea (4 patients, 14%); vomiting (3 patients, 10%); and abdominal pain, distension, and/or discomfort (2 patients, 7%). Gastrointestinal reactions contributed to the reasons for early discontinuation from the trial for 4 (14%) patients.

Absorption of concomitant oral medications may be affected in patients who develop diarrhea or vomiting.

To reduce the risk of gastrointestinal adverse events, patients should adhere to a low-fat diet supplying <20% of energy from fat and the dosage of JUXTAPID should be increased gradually *[see Dosage and Administration (2.1) and (2.2)]*.

5.6 Concomitant Use of CYP3A4 Inhibitors

CYP3A4 inhibitors increase the exposure of TRADNAME, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with JUXTAPID is contraindicated *[see Drug Interactions (7.1)]*. In the JUXTAPID clinical trials, one patient with HoFH developed markedly elevated transaminases (ALT 24x ULN, AST 13x ULN) within days of initiating the strong CYP3A4 inhibitor clarithromycin. If treatment with moderate or strong CYP3A4 inhibitors is unavoidable, JUXTAPID should be stopped during the course of treatment.

Grapefruit juice must be omitted from the diet while being treated with JUXTAPID.

Weak CYP3A4 inhibitors increase the exposure of JUXTAPID approximately 2-fold; therefore, JUXTAPID dosage should not exceed 30 mg daily when it is used concomitantly with these inhibitors, including atorvastatin and oral contraceptives *[see Dosage and Administration (2.3)* and *Drug Interactions (7.2)]*.

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5.7 Risk of Myopathy with Concomitant Use of Simvastatin or Lovastatin

The risk of myopathy, including rhabdomyolysis, with simvastatin and lovastatin monotherapy is dose related. Lomitapide approximately doubles the exposure to simvastatin; therefore, it is recommended to reduce the dose of simvastatin by 50% when initiating JUXTAPID *[see Clinical Pharmacology (12.3)]*. While taking JUXTAPID, limit simvastatin dosage to 20 mg daily (or 40 mg daily for patients who have previously tolerated simvastatin 80 mg daily for at least one year without evidence of muscle toxicity). Refer to the simvastatin prescribing information for additional dosing recommendations.

Interaction between lovastatin and lomitapide has not been studied. However, the metabolizing enzymes and transporters responsible for the disposition of lovastatin and simvastatin are similar, suggesting that JUXTAPID may increase the exposure of lovastatin; therefore, reducing the dose of lovastatin should be considered when initiating JUXTAPID.

5.8 Risk of Supratherapeutic or Subtherapeutic Anticoagulation with Warfarin

JUXTAPID increases the plasma concentrations of warfarin. Increases in the dose of JUXTAPID may lead to supratherapeutic anticoagulation, and decreases in the dose of JUXTAPID may lead to subtherapeutic anticoagulation. Difficulty controlling INR contributed to early discontinuation from the HoFH clinical trial for one of five patients taking concomitant warfarin. Patients taking warfarin should undergo regular monitoring of the INR, especially after any changes in JUXTAPID dosage. The dose of warfarin should be adjusted as clinically indicated *[see Drug Interactions (7.3)]*.

5.9 Risk of Malabsorption with Rare Hereditary Disorders of Galactose Intolerance

Patients with rare, hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should avoid JUXTAPID as this may result in diarrhea and malabsorption.

6 ADVERSE REACTIONS

The following important adverse reactions have been observed and are discussed in detail in other sections of the label:

- Risk of hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Reduced absorption of fat-soluble vitamins, and serum fatty acids *[see Warnings and Precautions (5.4)]*
- Gastrointestinal adverse reactions *[see Warnings and Precautions (5.5)]*

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6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

One single-arm, open-label, 78-week trial has been conducted in 29 patients with HoFH, 23 of whom completed at least one year of treatment. The initial dosage of JUXTAPID was 5 mg daily, with titration up to 60 mg daily during an 18-week period based on safety and tolerability. In this trial, the mean age was 30.7 years (range, 18 to 55 years), 16 (55%) patients were men, 25 (86%) patients were Caucasian, 2 (7%) were Asian, 1 (3%) was African American, and 1 (3%) was multi-racial *[see Clinical Studies (14)]*.

Five (17%) of the 29 patients with HoFH that participated in the clinical trial discontinued treatment due to an adverse reaction. The adverse reactions that contributed to treatment discontinuations included diarrhea (2 patients; 7%) and abdominal pain, nausea, gastroenteritis, weight loss, headache, and difficulty controlling INR on warfarin (1 patient each; 3%).

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

The adverse reactions reported in at least 10% of patients during the HoFH clinical trial are presented in Table 3.

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Table 3: Adverse Reactions Reported in ≥10% of Patients in the Clinical Trial in HoFH

ADVERSE REACTION	N (%)
Gastrointestinal Disorders	
Diarrhea	23 (79)
Nausea	19 (65)
Dyspepsia	11 (38)
Vomiting	10 (34)
Abdominal pain	10 (34)
Abdominal discomfort	6 (21)
Abdominal distension	6 (21)
Constipation	6 (21)
Flatulence	6 (21)
Gastroesophageal reflux disease	3 (10)
Defecation urgency	3 (10)
Rectal tenesmus	3 (10)
Infections	
Influenza	6 (21)
Nasopharyngitis	5 (17)
Gastroenteritis	4 (14)
Investigations	
Decreased weight	7 (24)
Increased ALT	5 (17)
General Disorders	
Chest pain	7 (24)
Fatigue	5 (17)
Fever	3 (10)
Musculoskeletal Disorders	
Back pain	4 (14)
Nervous System Disorders	
Headache	3 (10)
Dizziness	3 (10)
Respiratory Disorders	
Pharyngolaryngeal pain	4 (14)
Nasal congestion	3 (10)
Cardiac Disorders	
Angina pectoris	3 (10)
Palpitations	3 (10)

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Adverse reactions of severe intensity were reported by 8 (28%) of 29 patients, with the most common being diarrhea (4 patients, 14%), vomiting (3 patients, 10%), increased ALT or hepatotoxicity (3 patients, 10%), and abdominal pain, distension, and/or discomfort (2 patients, 7%).

Transaminase Elevations

During the HoFH clinical trial, 10 (34%) of 29 patients had at least one elevation in ALT and/or AST ≥3x ULN (see Table 4). No clinically meaningful elevations in total bilirubin or alkaline phosphatase were observed. Transaminases typically fell within one to four weeks of reducing the dose or withholding JUXTAPID.

Table 4: Patient Incidence of Transaminase Elevations During the HoFH Clinical Trial

	N (%)
Total Patients	29
Maximum ALT	
≥3 to <5 x ULN	6 (21%)
≥5 to <10 x ULN	3 (10%)
≥10 to <20 x ULN	1 (3%)
≥20x ULN	0
Maximum AST	
≥3 to <5 x ULN	5 (17%)
≥5 to <10 x ULN	1 (3%)
≥10 to <20 x ULN	0
≥20x ULN	0

Upper limits of normal (ULN) ranged from 33-41 international units/L for ALT and 36-43 international units/L for AST.

Among the 19 patients who enrolled in an extension study following the HoFH clinical trial, one discontinued because of increased transaminases that persisted despite several dose reductions, and one temporarily discontinued because of markedly elevated transaminases (ALT 24x ULN, AST 13x ULN) that had several possible causes, including a drug-drug interaction between JUXTAPID and the strong CYP3A4 inhibitor clarithromycin *[see Drug Interactions (7.1)]*.

Hepatic Steatosis

Hepatic fat was prospectively measured using magnetic resonance spectroscopy (MRS) in all eligible patients during the HoFH clinical trial. After 26 weeks, the median absolute increase in

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hepatic fat from baseline was 6%, and the mean absolute increase was 8% (range, 0% to 30%). After 78 weeks, the median absolute increase in hepatic fat from baseline was 6%, and the mean absolute increase was 7% (range, 0% to 18%). Among the 23 patients with evaluable data, on at least one occasion during the trial, 18 (78%) exhibited an increase in hepatic fat >5% and 3 (13%) exhibited an increase >20%. Data from individuals who had repeat measurements after stopping JUXTAPID show that hepatic fat accumulation is reversible, but whether histological sequelae remain is unknown.

7 DRUG INTERACTIONS

7.1 Moderate and Strong CYP3A4 Inhibitors

A strong CYP3A4 inhibitor has been shown to increase lomitapide exposure approximately 27-fold *[see Clinical Pharmacology (12.3)]*. Concomitant use of strong CYP3A4 inhibitors (such as boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) with lomitapide is contraindicated. Concomitant use of moderate CYP3A4 inhibitors (such as amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil) has not been studied, but concomitant use with lomitapide is contraindicated since lomitapide exposure will likely increase significantly in the presence of these inhibitors.

Patients must avoid grapefruit juice while taking JUXTAPID *[see Contraindications (4), Warnings and Precautions (5.6), and Clinical Pharmacology (12.3)]*.

7.2 Weak CYP3A4 Inhibitors

Weak CYP3A4 inhibitors increase lomitapide exposure approximately 2-fold *[see Clinical Pharmacology (12.3)]*. Lomitapide dosage should not exceed 30 mg daily when it is used concomitantly with weak CYP3A4 inhibitors (such as alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, lapatinib, nilotinib, oral contraceptives, pazopanib, ranitidine, ranolazine, tipranavir/ritonavir, ticagrelor, zileuton) *[see Dosage and Administration (2.3), Warnings and Precautions (5.6), and Clinical Pharmacology (12.3)]*.

7.3 Warfarin

Lomitapide increases plasma concentrations of both R(+)- warfarin and S(-)-warfarin by approximately 30% and increased the INR 22%. Patients taking warfarin should undergo regular

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monitoring of INR, particularly after any changes in lomitapide dosage. The dose of warfarin should be adjusted as clinically indicated *[see Warnings and Precautions (5.8)]*.

7.4 Simvastatin and Lovastatin

The risk of myopathy, including rhabdomyolysis, with simvastatin and lovastatin monotherapy is dose related. Lomitapide approximately doubles the exposure of simvastatin; therefore, the recommended dose of simvastatin should be reduced by 50% when initiating JUXTAPID *[see Clinical Pharmacology (12.3)]*. While taking JUXTAPID, limit simvastatin dosage to 20 mg daily (or 40 mg daily for patients who have previously tolerated simvastatin 80 mg daily for at least one year without evidence of muscle toxicity). Refer to the simvastatin prescribing information for simvastatin dosing recommendations.

Interaction between lovastatin and lomitapide has not been studied. However, the metabolizing enzymes and transporters responsible for the disposition of lovastatin and simvastatin are similar, suggesting that JUXTAPID may increase the exposure of lovastatin; therefore, reducing the dose of lovastatin should be considered when initiating JUXTAPID.

7.5 P-glycoprotein Substrates

Lomitapide is an inhibitor of P-glycoprotein (P-gp). Coadministration of lomitapide with P-gp substrates (such as aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan) may increase the absorption of P-gp substrates. Dose reduction of the P-gp substrate should be considered when used concomitantly with lomitapide.

7.6 Bile Acid Sequestrants

JUXTAPID has not been tested for interaction with bile acid sequestrants. Administration of JUXTAPID and bile acid sequestrants should be separated by at least 4 hours since bile acid sequestrants can interfere with the absorption of oral medications.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4)]*.

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Risk Summary

JUXTAPID is contraindicated during pregnancy because JUXTAPID may cause fetal harm when administered to a pregnant woman. Lomitapide was teratogenic in rats and ferrets at exposures estimated to be less than human therapeutic exposure at 60 mg (AUC = 67 ng*h/mL) when administered during organogenesis. There was no evidence of teratogenicity in rabbits at 3 times the maximum recommended human dose (MRHD) of 60 mg based on body surface area. Embryo-fetal lethality was observed in rabbits at 6-times the MRHD. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Animal Data

Oral gavage doses of 0.04, 0.4, or 4 mg/kg/day lomitapide given to pregnant rats from gestation day 6 through organogenesis were associated with fetal malformations at ≥2-times human exposure at the MRHD (60 mg) based on plasma AUC comparisons. Fetal malformations included umbilical hernia, gastroschisis, imperforate anus, alterations in heart shape and size, limb malrotations, skeletal malformations of the tail, and delayed ossification of cranial, vertebral and pelvic bones.

Oral gavage doses of 1.6, 4, 10, or 25 mg/kg/day lomitapide given to pregnant ferrets from gestation day 12 through organogenesis were associated with both maternal toxicity and fetal malformations at exposures that ranged from less than the human exposure at the MRHD to 5-times the human exposure at the MRHD. Fetal malformations included umbilical hernia, medially rotated or short limbs, absent or fused digits on paws, cleft palate, open eye lids, low-set ears, and kinked tail.

Oral gavage doses of 0.1, 1, or 10 mg/kg/day lomitapide given to pregnant rabbits from gestation day 6 through organogenesis were not associated with adverse effects at systemic exposures up to 3-times the MRHD of 60 mg based on body surface area comparison. Treatment at doses of ≥20 mg/kg/day, ≥6-times the MRHD, resulted in embryo-fetal lethality.

Pregnant female rats given oral gavage doses of 0.1, 0.3, or 1 mg/kg/day lomitapide from gestation day 7 through termination of nursing on lactation day 20 were associated with malformations at systemic exposures equivalent to human exposure at the MRHD of 60 mg based on AUC. Increased pup mortality occurred at 4-times the MRHD.

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8.3 Nursing Mothers

It is not known whether lomitapide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for lomitapide in a 2-year mouse study, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use

Clinical studies of JUXTAPID did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dosing for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Females of Reproductive Potential

JUXTAPID may cause fetal harm *[see Use in Specific Populations (8.1)]*. Females who become pregnant during JUXTAPID therapy should stop JUXTAPID immediately and notify their healthcare provider.

Pregnancy testing

Females of reproductive potential should have a negative pregnancy test before starting JUXTAPID.

Contraception

Females of reproductive potential should use effective contraception during JUXTAPID therapy. The recommended maximum dosage of JUXTAPID is 30 mg daily with concomitant use of oral contraceptives, since oral contraceptives are weak CYP3A4 inhibitors *[see Drug Interactions (7.2)]*. Hormone absorption from oral contraceptives may be incomplete if vomiting or diarrhea occurs while taking JUXTAPID, warranting the use of additional contraceptive methods *[see Warnings and Precautions (5.5)]*.

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8.7 Renal Impairment

Patients with end-stage renal disease receiving dialysis should not exceed 40 mg daily since lomitapide exposure in these patients increased approximately 50% compared with healthy volunteers. Effects of mild, moderate, and severe renal impairment, including those with end-stage renal disease not yet receiving dialysis, on lomitapide exposure have not been studied. However, it is possible that patients with renal impairment who are not yet receiving dialysis may experience increases in lomitapide exposure exceeding 50% *[see Clinical Pharmacology (12.3)]*.

8.8 Hepatic Impairment

Patients with mild hepatic impairment (Child-Pugh A) should not exceed 40 mg daily since the lomitapide exposure in these patients increased approximately 50% compared with healthy volunteers. JUXTAPID is contraindicated in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment since the lomitapide exposure in patients with moderate hepatic impairment increased 164% compared with healthy volunteers *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

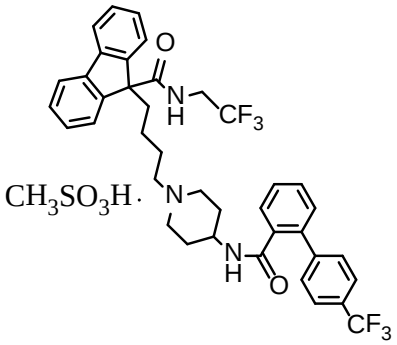
There is no specific treatment in the event of overdose of JUXTAPID. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Liver-related tests should be monitored. Hemodialysis is unlikely to be beneficial given that lomitapide is highly protein bound.

11 DESCRIPTION

JUXTAPID capsules contain lomitapide mesylate, a synthetic lipid-lowering agent for oral administration.

The chemical name of lomitapide mesylate is N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9*H*-fluorene-9-carboxamide, methanesulfonate salt. Its structural formula is:

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The empirical formula for lomitapide mesylate is $C_{39}H_{37}F_6N_3O_2 \bullet CH_4O_3S$ and its molecular weight is 789.8.

Lomitapide mesylate is a white to off-white powder that is slightly soluble in aqueous solutions of pH 2 to 5. Lomitapide mesylate is freely soluble in acetone, ethanol, and methanol; soluble in 2-butanol, methylene chloride, and acetonitrile; sparingly soluble in 1-octanol and 2-propanol; slightly soluble in ethyl acetate; and insoluble in heptane.

Each JUXTAPID capsule contains lomitapide mesylate equivalent to 5, 10, or 20 mg lomitapide free base and the following inactive ingredients: pregelatinized starch, sodium starch glycolate, microcrystalline cellulose, lactose monohydrate, silicon dioxide and magnesium stearate. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide. The imprinting ink contains shellac, black iron oxide, and propylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

12.2 Pharmacodynamics

Effects on QT Interval

At a concentration 23 times the C_{max} of the maximum recommended dose, lomitapide does not prolong QTc to any clinically relevant extent.

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12.3 Pharmacokinetics

Absorption

Upon oral administration of a single 60-mg dose of JUXTAPID, the lomitapide t_{max} is around 6 hours in healthy volunteers. The absolute bioavailability of lomitapide is approximately 7%. Lomitapide pharmacokinetics is approximately dose-proportional for oral single doses from 10-100 mg.

Distribution

The mean lomitapide volume of distribution at steady state is 985-1292 liters. Lomitapide is 99.8% plasma-protein bound.

Metabolism

Lomitapide is metabolized extensively by the liver. The metabolic pathways include oxidation, oxidative N-dealkylation, glucuronide conjugation, and piperidine ring opening. Cytochrome P450 (CYP) 3A4 metabolizes lomitapide to its major metabolites, M1 and M3, as detected in plasma. The oxidative N-dealkylation pathway breaks the lomitapide molecule into M1 and M3. M1 is the moiety that retains the piperidine ring, whereas M3 retains the rest of the lomitapide molecule in vitro. CYPs 1A2, 2B6, 2C8, and 2C19 may metabolize lomitapide to a small extent to M1. M1 and M3 do not inhibit activity of microsomal triglyceride transfer protein *in vitro*.

Excretion

In a mass-balance study, a mean of 59.5% and 33.4% of the dose was excreted in the urine and feces, respectively. In another mass-balance study, a mean of 52.9% and 35.1% of the dose was excreted in the urine and feces, respectively. Lomitapide was not detectable in urine samples. M1 is the major urinary metabolite. Lomitapide is the major component in the feces. The mean lomitapide terminal half-life is 39.7 hours.

Specific Populations

Hepatic Impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of 60 mg lomitapide in healthy volunteers with normal hepatic function compared with patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment. In patients with moderate hepatic impairment, lomitapide AUC and C_{max} were 164% and 361% higher, respectively,

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compared with healthy volunteers. In patients with mild hepatic impairment, lomitapide AUC and C_{max} were 47% and 4% higher, respectively, compared with healthy volunteers. Lomitapide has not been studied in patients with severe hepatic impairment (Child-Pugh score 10-15) *[see Dosage and Administration (2.6), Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.8)]*.

Renal Impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of 60 mg lomitapide in patients with end-stage renal disease receiving hemodialysis compared with healthy volunteers with normal renal function. Healthy volunteers had estimated creatinine clearance >80 mL/min by the Cockcroft-Gault equation. Compared with healthy volunteers, lomitapide $AUC_{0\text{-}inf}$ and C_{max} were 40% and 50% higher, respectively, in patients with end-stage renal disease receiving hemodialysis. Effects of mild, moderate, and severe renal impairment as well as end-stage renal disease not yet on dialysis on lomitapide exposure have not been studied *[see Dosage and Administration (2.5) and Use in Specific Populations (8.7)]*.

Drug Interactions

[see Dosage and Administration (2.3), Contraindictions (4), Warnings and Precautions (5.6), (5.7), (5.8), and Drug Interactions (7)].

In vitro Assessment of Drug Interactions

Lomitapide does not induce CYPs 1A2, 3A4, or 2B6. Lomitapide inhibits CYP3A4. Lomitapide does not inhibit CYPs 1A2, 2B6, 2C9, 2C19, 2D6, or 2E1. M1 and M3 do not induce CYPs 1A2, 3A4, or 2B6. M1 and M3 do not inhibit CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4. Lomitapide is not a P-gp substrate. Lomitapide inhibits P-gp but does not inhibit breast cancer resistance protein (BCRP).

Effects of other Drugs on Lomitapide

Table 5 summarizes the effect of coadministered drugs on lomitapide AUC and C_{max}.

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Table 5: Effect of Coadministered Drugs on Lomitapide Systemic Exposure

Coadministered Drug	Dosing Of Coadministered Drug	Dosing of Lomitapide	Ratio of Lomitapide Exposure With/Without Coadministered Drug No Effect = 1		
				AUC	C_{max}
Contraindicated with lomitapide *[see Contraindications (4) and Warnings and Precautions (5.6)]*					
Ketoconazole	200 mg BID for 9 days	60 mg QD		↑ 27	↑ 15

BID = twice daily; QD = once daily
↑ = increase

CYP3A4 Inhibitors

Lomitapide exposure increased 27-fold in the presence of ketoconazole, a strong CYP3A4 inhibitor. Thus, concomitant use of strong CYP3A4 inhibitors and lomitapide is contraindicated. The effect of moderate CYP3A4 inhibitors on lomitapide exposure has not been studied. However, moderate CYP3A4 inhibitors will likely increase lomitapide exposure significantly based on the results of concomitant use of strong and weak CYP3A4 inhibitors *[see Drug Interactions (7.1) and (7.2)]*. Thus, concomitant use of moderate CYP3A4 inhibitors and lomitapide is contraindicated.

Interaction between weak CYP3A4 inhibitors and lomitapide has not been studied. Based on cross-studies comparisons, the lomitapide exposure approximately doubles in the presence of oral contraceptives, which are weak CYP3A4 inhibitors. Do not exceed 30 mg daily of JUXTAPID when used concomitantly with weak CYP3A4 inhibitors. *[See Dosage and Administration (2.3) and Drug Interactions (7.2)]*.

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Effect of Lomitapide on other Drugs

Table 6 summarizes the effects of lomitapide on the AUC and C_{max} of coadministered drugs.

Table 6: Effect of Lomitapide on the Systemic Exposure of Coadministered Drugs

COADMINISTERED DRUG	DOSING OF COADMINISTERED DRUG	DOSING OF LOMITAPIDE	CHANGE OF COADMINISTERED DRUG EXPOSURE WITH / WITHOUT LOMITAPIDE)		
				AUC	C_{max}
Dosage adjustment necessary when coadministered with lomitapide					
Simvastatin[a]	40 mg single dose	60 mg QD × 7 days	Simvastatin Simvastatin acid	↑ 99% ↑ 71%	↑ 102% ↑ 57%
	20 mg single dose	10 mg QD x 7 days	Simvastatin Simvastatin acid	↑ 62% ↑ 39%	↑65% ↑ 35%
Warfarin[b]	10 mg single dose	60 mg QD x 12 days	R(+) warfarin S(-) warfarin INR	↑ 28% ↑ 30% ↑ 7%	↑ 14% ↑ 15% ↑ 22%
No dosing adjustments required for the following:					
Atorvastatin	20 mg 20 mg	60 mg QD × 7 days 10 mg QD × 7 days	Atorvastatin acid Atorvastatin acid	↑ 52% ↑ 11%	↑63% ↑19%
Rosuvastatin	20 mg 20 mg	60 mg QD × 7 days 10 mg QD × 7 days	Rosuvastatin Rosuvastatin	↑ 32% ↑ 2%	↑ 4% ↑ 6%
Fenofibrate, micronized	145 mg	10 mg QD × 7 days	Fenofibric acid	↓ 10%	↓29%
Ezetimibe	10 mg	10 mg QD × 7 days	Total ezetimibe	↑ 6%	↑ 3%
Extended release niacin	1000 mg	10 mg QD × 7 days	Nicotinic acid Nicotinuric acid	↑ 10% ↓ 21%	↑ 11% ↓ 15%

[a] Limit simvastatin dosage to 20 mg daily (or 40 mg daily for patients who have previously tolerated simvastatin 80 mg daily for at least one year without evidence of muscle toxicity). Refer to the simvastatin prescribing information for additional dosing recommendations.

[b] Patients taking warfarin should undergo regular monitoring of the INR, especially after any changes in lomitapide dosage.

QD = once daily; INR = international normalized ratio; ↑ = increase; ↓ = decrease

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year dietary carcinogenicity study in mice, lomitapide was administered at doses of 0.3, 1.5, 7.5, 15, or 45 mg/kg/day. There were statistically significant increases in the incidences of liver adenomas and carcinomas in males at doses ≥1.5 mg/kg/day (≥2-times the MRHD at 60 mg

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based on AUC) and in females at ≥7.5 mg/kg/day (≥10-times the human exposure at 60 mg based on AUC). Incidences of small intestinal carcinomas in males and combined adenomas and carcinomas in females were significantly increased at doses ≥15 mg/kg/day (≥23-times the human exposure at 60 mg based on AUC).

In a 2-year carcinogenicity study in rats, lomitapide was administered by oral gavage for up to 99 weeks at doses of 0.25, 1.7, or 7.5 mg/kg/day in males and 0.03, 0.35, or 2.0 mg/kg/day in females. While the design of the study was suboptimal, there were no statistically significant drug-related increases in tumor incidences at exposures up to 6-times (males) and 8-times (females) higher than human exposure at the MRHD based on AUC.

Lomitapide did not exhibit genotoxic potential in a battery of studies, including the *in vitro* Bacterial Reverse Mutation (Ames) assay, an *in vitro* cytogenetics assay using primary human lymphocytes, and an oral micronucleus study in rats.

Lomitapide had no effect on fertility in rats at doses up to 5 mg/kg/day at systemic exposures estimated to be 4-times (females) and 5-times (males) higher than in humans at 60 mg based on AUC.

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14 CLINICAL STUDIES

The safety and effectiveness of JUXTAPID as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, were evaluated in a multinational, single-arm, open-label, 78-week trial involving 29 adults with HoFH. 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, or (2) skin fibroblast LDL receptor activity <20% normal, or (3) untreated TC >500 mg/dL and TG <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 four patients meeting BMI criteria for obesity; one patient had type 2 diabetes. Concomitant lipid-lowering treatments at baseline included one or more of the following: statins (93%), ezetimibe (76%), nicotinic acid (10%), bile acid sequestrant (3%), and fibrate (3%); 18 (62%) were receiving apheresis.

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

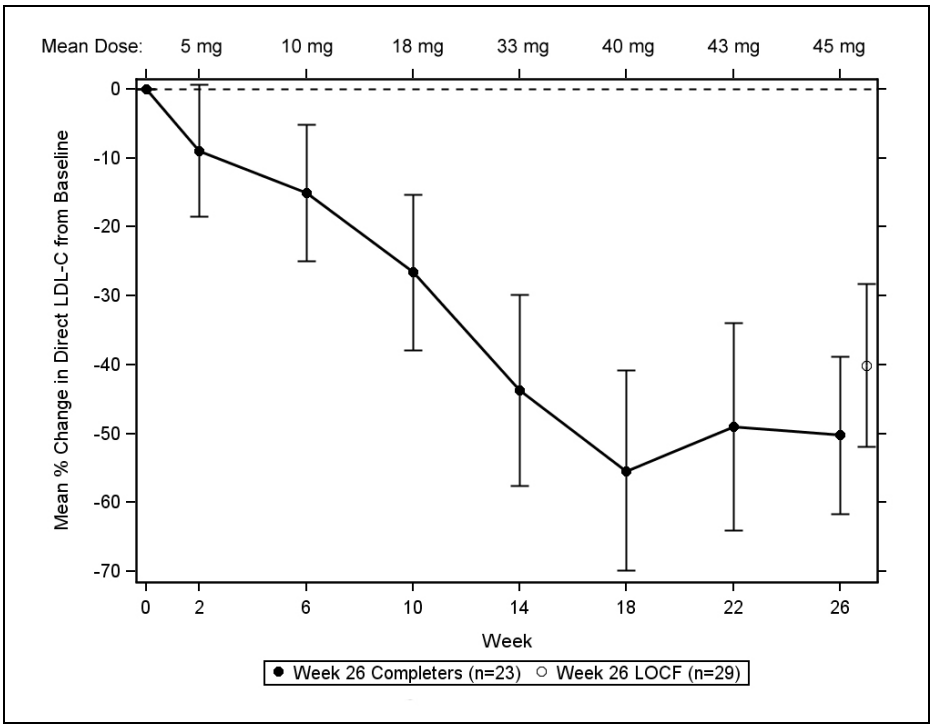
Twenty-three (79%) patients completed the efficacy endpoint at Week 26, all of whom went on to complete 78 weeks of treatment. Adverse events contributed to premature discontinuation for five patients *[see Adverse Reactions (6.1)]*. The maximum tolerated doses during the efficacy period were 5 mg (10%), 10 mg (7%), 20 mg (21%), 40 mg (24%), and 60 mg (34%).

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

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observation carried forward (LOCF) for patients who discontinued prematurely. The mean percent change in LDL-C from baseline through Week 26 is shown in Figure 1 for the 23 patients who completed the efficacy period.

Figure 1: Mean Percent Change in LDL-C from Baseline (Week 26 Completers)



Error bars represent 95% confidence intervals of the mean.

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Changes in lipids and lipoproteins through the efficacy endpoint at Week 26 are presented in Table 7.

Table 7: Absolute Values and Percent Changes from Baseline in Lipids and Lipoproteins

PARAMETER	BASELINE	WEEK 26/LOCF (N=29)	
	Mean (SD)	Mean (SD)	Mean % Change
LDL-C, direct (mg/dL)	336 (114)	190 (104)	-40 *
TC (mg/dL)	430 (135)	258 (118)	-36 *
apo B (mg/dL)	259 (80)	148 (74)	-39 *
Non-HDL-C (mg/dL)	386 (132)	217 (113)	-40
VLDL-C (mg/dL)	21 (10)	13 (9)	-29
TG (mg/dL)[a]	92 [72, 128]	57 [36, 78]	-45 *
HDL-C (mg/dL)	44 (11)	41 (13)	-7

[a] Median values with interquartile range and median % change presented for TG.
* Statistically significant compared with baseline based on the pre-specified gatekeeping method for controlling Type I error among the primary and key secondary endpoints.

After week 26, during the safety phase of the study, adjustments to concomitant lipid-lowering treatments were allowed. For the study population overall, average reductions in LDL-C, TC, apo B, and non-HDL-C were sustained during chronic therapy.

16 HOW SUPPLIED / STORAGE AND HANDLING

5 mg capsules:
Orange/orange hard gelatin capsule printed with black ink “A733” and “5 mg”
Bottles of 28 NDC 76431-105-01

10 mg capsules:
Orange/white hard gelatin capsule printed with black ink “A733” and “10 mg”
Bottles of 28 NDC 76431-110-01

20 mg capsules:
White/white hard gelatin capsule printed with black ink “A733” and “20 mg”
Bottles of 28 NDC 76431-120-01

Storage: Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (between 59°F and 86°F). Brief exposure to temperatures up to 40°C (104°F) may be tolerated provided the mean kinetic temperature does not exceed 25°C (77°F); however, such exposure should be minimized. Keep container tightly closed and protect from moisture.

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17 PATIENT COUNSELING INFORMATION

See FDA-approved labeling (Medication Guide)

Patients should be informed that a registry for patients taking JUXTAPID has been established in order to monitor and evaluate the long-term effects of JUXTAPID. Patients are encouraged to participate in the registry and should be informed that their participation is voluntary. For information regarding the registry program visit www.JUXTAPID.com.

Advise patients of the following:

Risk of Hepatotoxicity *[see Warnings and Precautions (5.1)]*

- JUXTAPID can cause both elevations in transaminases and hepatic steatosis. Discuss with the patient the importance of monitoring of liver-related tests before taking JUXTAPID, prior to each dose escalation, and periodically thereafter.
- Patients should be advised of the potential for increased risk of liver injury if alcohol is consumed while taking JUXTAPID. It is recommended that patients taking JUXTAPID limit consumption to not more than one alcoholic drink per day.
- JUXTAPID is commonly associated with nausea, vomiting, and abdominal pain. Advise patients to promptly report these symptoms if they increase in severity, persist, or change in the character, as they might reflect liver injury. Patients should also report any other symptoms of possible liver injury, including fever, jaundice, lethargy, or flu-like symptoms.

JUXTAPID REMS PROGRAM *[see Warnings and Precautions (5.2)]*

- JUXTAPID is only available through a restricted program called JUXTAPID REMS PROGRAM and therefore, JUXTAPID is only available from certified pharmacies that are enrolled in the program.

Females of Reproductive Potential *[see Warnings and Precautions (5.3)]*

- JUXTAPID is contraindicated in pregnancy.
- Advise females of reproductive potential that they should have a negative pregnancy test before starting JUXTAPID and that they should use effective contraception while taking JUXTAPID. If oral contraceptives are initiated while taking JUXTAPID, the dose of JUXTAPID may require adjustment. Hormone absorption from oral contraceptives may be incomplete if vomiting or diarrhea occurs while taking JUXTAPID, warranting the use of additional contraceptive methods.
- Nursing Mothers: A decision should be made whether to discontinue nursing or discontinue JUXTAPID.

Dietary Supplements *[see Warnings and Precautions (5.4)]*

- Discuss with the patient the importance of taking daily supplements that contain 400 international units vitamin E and at least 200 mg linoleic acid, 210 mg alpha-linolenic acid (ALA), 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA)

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Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.5)]*

- Inform the patient that gastrointestinal adverse reactions are common with JUXTAPID. These include, but are not limited to, diarrhea, nausea/vomiting, abdominal pain/discomfort, flatulence, and constipation. Strict adherence to a low-fat diet (<20% of total calories from fat) may reduce these reactions.
- Tell the patient that taking JUXTAPID with food may adversely impact gastrointestinal tolerability; therefore, they should take JUXTAPID at least 2 hours after the evening meal, swallowing each capsule whole.
- Absorption of oral medications may be affected in patients who develop diarrhea or vomiting. For example, hormone absorption from oral contraceptives may be incomplete, warranting the use of additional contraceptive methods. Patients who develop these symptoms should seek advice from their healthcare provider.

Drug Interactions *[see Warnings and Precautions (5.6) and Drug Interactions (7)]*

- Tell the patient to omit grapefruit juice from his/her diet while on JUXTAPID.
- Because multiple drug-drug interactions have been described with JUXTAPID, advise the patient to tell their healthcare provider(s) about all medications, nutritional supplements, and vitamins that they are taking or may be taking while taking JUXTAPID.

Missed Doses

- If a dose of JUXTAPID is missed, the normal dose should be taken at the usual time the next day. If dosing is interrupted for more than a week, tell the patient to contact their healthcare provider before restarting treatment.

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MEDICATION GUIDE

JUXTAPID™ (JUKS-tuh-pid)

(lomitapide)

capsules

Read this Medication Guide before your treatment.

What is the most important information I should know about JUXTAPID?

- JUXTAPID is available only through certified pharmacies that are enrolled in the JUXTAPID REMS Program. Your doctor must be enrolled in the program in order for you to be prescribed JUXTAPID.

There is a registry that collects information about the effects of taking JUXTAPID over time. Ask your doctor for more information about this registry or visit www.JUXTAPID.com.

JUXTAPID may cause serious side effects including:

1. **Liver problems.** JUXTAPID can cause liver problems.
   - Your doctor should do blood tests to check your liver before you start JUXTAPID, if your dose is increased, and while you take JUXTAPID. If your tests show some liver problems, your doctor may adjust your dose of JUXTAPID or stop it altogether.
   - Tell your doctor if you have had liver problems, including liver problems while taking other medicines.
   - JUXTAPID may cause nausea, vomiting and stomach pain, especially if you do not eat a low-fat diet. These side effects can also be symptoms of liver problems. Tell your doctor right away if you have any of these symptoms of liver problems while taking JUXTAPID:
     - nausea, vomiting or stomach pain that gets worse, does not go away, or changes
     - fever
     - yellowing of your eyes or skin
     - you are more tired than usual
     - flu-like symptoms
   - Drinking alcohol may increase your chance of having liver problems or make your liver problems worse. You should not have more than 1 alcoholic drink each day while taking JUXTAPID.
2. **Harm to your unborn baby.** JUXTAPID may cause harm to your unborn baby.
   - If you are pregnant, think you may be pregnant, or are planning to become pregnant, **do not** take JUXTAPID.
   - If you are a female who can get pregnant, you should have a pregnancy test before you start taking JUXTAPID. Your pregnancy test must be negative for you to get JUXTAPID.
     - **Do not** have sex while taking JUXTAPID unless you are using effective birth control.
     - Talk with your doctor or nurse to find the best method of birth control for you.
     - Birth control pills may not work as well if you have diarrhea or vomiting.

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- If you start taking birth control pills while you are taking JUXTAPID, tell your doctor. Your doctor might need to change your dose of JUXTAPID.

- If you become pregnant while taking JUXTAPID, stop taking JUXTAPID and call your doctor right away.

What is JUXTAPID?

JUXTAPID is a prescription medicine used along with diet and other lipid-lowering treatments, including low-density lipoprotein (LDL) apheresis where available, in people with homozygous familial hypercholesterolemia (HoFH) to reduce:

- LDL ("bad") cholesterol
- total cholesterol
- a protein that carries "bad" cholesterol in the blood (apolipoprotein B)
- non-high-density lipoprotein cholesterol (non-HDL-C)

It is not known if JUXTAPID can decrease problems from high cholesterol, such as heart attack, stroke, death or other health problems.

It is not known if JUXTAPID is safe in people with high cholesterol but who do not have HoFH.

JUXTAPID should not be taken with certain medicines or food. You should not drink grapefruit juice. Ask your doctor or pharmacist to make sure you can take JUXTAPID with your other medicines, and tell your doctor about any new medicines you might take even for only a short time.

It is not known if JUXTAPID is safe and effective in people with kidney problems including people with end-stage kidney disease who are not on dialysis.

It is not known if JUXTAPID is safe and effective when used in children under the age of 18.

Who should not take JUXTAPID?

Do not take JUXTAPID if you:

- are pregnant, think you may be pregnant, or are planning to become pregnant. See **"What is the most important information I should know about JUXTAPID?"**
- take medicines that affect how the body breaks down JUXTAPID (that is, strong or moderate CYP3A4 inhibitors). Check with your doctor and/or pharmacist to see if you are taking any of these medications. These may include certain medications intended to treat bacterial, fungal or viral infections, and medications to treat depression, high blood pressure, or angina.
- drink grapefruit juice
- have moderate or severe liver problems or active liver disease, including people who have unexplained abnormal liver tests.

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What should I tell my doctor before taking JUXTAPID?

Before you take JUXTAPID, tell your doctor if you:

- have liver problems
- have kidney problems
- have intestine or bowel problems
- drink alcohol
- are breastfeeding or plan to breastfeed. It is not known if JUXTAPID passes into your breast milk. You and your doctor should decide if you will take JUXTAPID or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Before starting a new medicine while taking JUXTAPID, even if you will only be taking it for a short time, ask your doctor or pharmacist if it is safe to take with JUXTAPID.

JUXTAPID may affect the way other medicines work, and other medicines may affect how JUXTAPID works.

Certain medicines can affect how your liver breaks down other medicines.

Especially tell your doctor if you take:

- a blood thinner called warfarin
- medicines for high cholesterol, including statins such as atorvastatin or simvastatin, and resins such as colesevelam or cholestyramine
- medicines for bacteria, fungus, or viral infection (including HIV and hepatitis C)
- medicines for depression, high blood pressure, or angina
- birth control pills

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take JUXTAPID?

- Take JUXTAPID exactly as your doctor tells you to take it.
- Your doctor will tell you how much JUXTAPID to take and when to take it.
- Your doctor may change your dose of JUXTAPID if needed.
- Do not change your JUXTAPID dose yourself.
- Take JUXTAPID 1 time each day at least 2 hours after your evening meal.
- Take JUXTAPID with water.
- You should not take JUXTAPID with food. Taking JUXTAPID with food may cause stomach problems.
- Take JUXTAPID capsules whole. Do not open, crush, dissolve, or chew capsules before swallowing. If you cannot swallow JUXTAPID capsules whole, tell your doctor. You may need a different medicine.
- If you take a medicine that lowers cholesterol by binding bile acids, such as colesevelam or cholestyramine, take it at least 4 hours before or 4 hours after you take JUXTAPID. Ask your doctor if you are not sure if you take these medicines.
- To help lower the chance of stomach problems, stay on a low-fat diet. Ask your doctor about talking to a dietician to learn what you should eat while taking JUXTAPID. JUXTAPID makes it harder for some nutrients to get into your body. Take Vitamin E and fatty acids each day while you take JUXTAPID. Ask your doctor, nurse, or dietician how to add them to your diet.
- If you take too much JUXTAPID, call your doctor right away.

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- Do not stop JUXTAPID unless your doctor tells you to stop it.
- If you miss a dose of JUXTAPID, take your usual dose the next day at the usual time. If you stop taking JUXTAPID for more than a week, talk to your doctor before restarting treatment.

What are the possible side effects of JUXTAPID?

JUXTAPID can cause serious side effects, including:

- **liver problems.** See **"What is the most important information I should know about JUXTAPID?"**
- **harm to your unborn baby.** See **"What is the most important information I should know about JUXTAPID?"**
- **gastrointestinal symptoms.** Diarrhea, nausea/vomiting, and stomach pain/discomfort are very common with JUXTAPID. Strictly following a low-fat diet may help lower the chance of having these symptoms.
- **problems absorbing certain nutrients.** JUXTAPID may decrease your ability to absorb fat-soluble nutrients such as Vitamin E and fatty acids. You should take supplements each day that contain fat-soluble vitamins. People with bowel or pancreas problems may have an increased chance of not being able to absorb these nutrients. See **"How should I take JUXTAPID?"**
- **increased levels of certain blood thinners.** JUXTAPID can increase the level of the blood thinner, warfarin. If you take warfarin, your doctor should check your blood clotting times frequently, especially after your dose of JUXTAPID changes.
- **liver problems caused by certain drugs.** Certain medicines can cause liver problems, including isotretinoin, acetaminophen, methotrexate, tetracyclines, and tamoxifen. If you take these medicines with JUXTAPID your doctor may do blood tests more often to check your liver.

The most common side effects of JUXTAPID include:

- diarrhea (loose stool)
- nausea
- vomiting
- stomach cramping or pain
- indigestion
- gas

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of JUXTAPID. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store JUXTAPID?

- Store JUXTAPID at room temperature, between 68°F and 77°F (20°C and 25°C).
- Keep JUXTAPID in a tightly closed container.
- Keep JUXTAPID capsules dry.

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- Safely throw away medicine that is out of date or no longer needed.

Keep JUXTAPID and all medicines out of the reach of children.

General information about the safe and effective use of JUXTAPID

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use JUXTAPID for a condition for which it was not prescribed. Do not give JUXTAPID to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about JUXTAPID. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about JUXTAPID that is written for healthcare professionals.

For more information, go to www.JUXTAPID.com or call 1-85-JUXTAPID (1-855-898-2743).

What are the ingredients in JUXTAPID?

Active ingredient: lomitapide

Inactive ingredients: pregelatinized starch, sodium starch glycolate, microcrystalline cellulose, lactose monohydrate, silicon dioxide, magnesium stearate

Capsule shell: gelatin, titanium dioxide, edible black ink for printing and may contain red iron oxide

This Medication Guide has been approved by the U.S. Food and Drug Administration.

JUXTAPID is a trademark of Aegerion Pharmaceuticals, Inc.

Manufactured for:

Aegerion Pharmaceuticals, Inc.
Cambridge, MA 02142

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