



## Starter Kit

### Important Safety Information about Juxtapid

#### INDICATION:

Juxtapid® (lomitapide) 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).

#### LIMITATIONS OF USE:

The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH). The effect of JUXTAPID on cardiovascular morbidity and mortality has not been determined.

#### 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)  $\geq 3\times$  upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR), or alkaline phosphatase.

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.

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  $\geq 3\times$  ULN. Discontinue JUXTAPID for clinically significant liver toxicity. 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.

Prescribe JUXTAPID only to patients with a clinical or laboratory diagnosis consistent with HoFH. The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.



# Juxtapid®: The first FDA-approved adjunct treatment for Homozygous Familial Hypercholesterolemia (HoFH)

## What's inside



### Getting a patient started on Juxtapid

- REMS training
- Patient enrollment form
- Rx form



### Juxtapid Prior Authorization and Access Guide

- Medical necessity letter template
- Appeal letter template



### Juxtapid Dosing and Administration Guide



### Copay Support Information

Please refer to the full Terms and Conditions in the back pocket for additional eligibility requirements.



### US Prescribing Information



### Contact Information Card



SCAN THE QR CODE  
FOR THE DIGITAL RX FORM



**BY PHONE**  
1-855-898-2743



**BY FAX**  
1-855-898-2498



**HOURS OF OPERATION**  
Monday to Friday 8:00 am – 8:00 pm  
(Eastern Standard Time)

For more information, visit [chiesitotalcare.com](https://chiesitotalcare.com)

Chiesi Total Care Program offered through Accredo Specialty Pharmacy.  
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### CONTRAINDICATIONS:

- Pregnancy
- Concomitant administration of moderate or strong CYP3A4 inhibitors
- Moderate or severe hepatic impairment or active liver disease including unexplained persistent elevations of serum transaminases

### WARNINGS AND PRECAUTIONS

JXTAPID can cause elevations in transaminases and hepatic steatosis. Although cases of hepatic failure have not been reported, there is concern that JXTAPID could induce steatohepatitis, which can progress to cirrhosis over several years. Modify the dose of JXTAPID if elevations of transaminases are observed and discontinue JXTAPID for persistent or clinically significant elevations. 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  $\geq 2\times$  ULN, or active liver disease, discontinue treatment with JXTAPID and identify the probable cause. Use JXTAPID with caution when co-administered with agents known to be hepatotoxic. Alcohol may

increase levels of hepatic fat and induce or exacerbate liver injury.

Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment. 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.

JXTAPID may cause fetal harm when administered to a pregnant woman. Females of reproductive potential should have a negative pregnancy test before starting JXTAPID and should use effective contraception during therapy with JXTAPID. The recommended maximum dosage of JXTAPID is 40 mg daily when used concomitantly with oral contraceptives.

Given its mechanism of action in the small intestine, JXTAPID may reduce the absorption of fat-soluble nutrients. Patients treated with JXTAPID 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).

Gastrointestinal adverse reactions are common and may lead to treatment discontinuation. Instruct patients to stop JXTAPID and contact their healthcare provider if severe diarrhea occurs, or if they experience symptoms of volume depletion such as lightheadedness, decreased urine output, or tiredness. In such cases, consider reducing the dose or suspending use of JXTAPID. To reduce the risk of gastrointestinal adverse reactions, patients should adhere to a low-fat diet supplying less than 20% of energy from fat and the dosage of JXTAPID should be increased gradually.

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Avoid use of JXTAPID in patients with rare hereditary diseases of galactose intolerance.

### ADVERSE REACTIONS:

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### REPORTING OF ADVERSE REACTIONS:

All healthcare professionals should report all suspected adverse reactions. Please contact Chiesi Farmaceutici S.p.A. at 1-888-661-9260 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.**

For more information, visit [juxtapid.com](http://juxtapid.com).

**Chiesi Total Care<sup>SM</sup> Program offered through Accredo Specialty Pharmacy.**

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Juxtapid® is a registered trademark owned by the Chiesi Group.

Chiesi Total Care<sup>SM</sup> is a service mark of CHIESI FARMACEUTICI S.p.A.

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## Getting Started Guide

To get a patient started on Juxtapid® follow 3 steps outlined in this guide.

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Visit [chiesitotalcare.com](https://chiesitotalcare.com) or call 1-855-898-2743. We're ready to help!





## STEP 1

### REMS Training



## Complete Risk Evaluation and Mitigation Strategy (REMS) training

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.**

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of a drug outweigh its risks.

### To complete your REMS Prescriber Certification:

- Review the JUXTAPID Prescribing Information and the Fact Sheet
- Visit the Juxtapid REMS program website to complete the online prescriber training module and THEN FAX THE PRESCRIBER ENROLLMENT FORM to 1- 855-898-2498.

**Counsel each new patient on the risk of hepatotoxicity and the need for baseline and periodic monitoring using the Patient Guide. Complete a Patient-Prescriber Acknowledgement Form with each patient.**



Scan the QR code  
to visit the site.

## STEP 2

### Prescription



## Fill out the Prescription Forms

A prescription for Juxtapid can only be written on the Juxtapid REMS Authorization Form. Complete, sign, and fax the completed form to 1-855-898-2498



Scan the QR code  
to download  
the form.

## IMPORTANT SAFETY INFORMATION

### ADVERSE REACTIONS:

The most common adverse reactions were gastrointestinal, reported by 27 (93%) of 29 patients. Adverse reactions reported by 8 (28%) or more 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.

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**Juxtapid<sup>®</sup>**  
(lomitapide) capsules

## PRESCRIBER ATTESTATION

### By signing this form, I attest that:

- JUXTAPID® (lomitapide) capsules are only available through the JUXTAPID REMS and that I must comply with the program requirements in order to prescribe JUXTAPID.
- I have reviewed the **Prescribing Information, Fact Sheet** and **Prescriber Training Module**.
- Successfully completed the **Prescriber Knowledge Assessment** and submitted it to the JUXTAPID REMS.

### Use:

- I understand that JUXTAPID is only 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).
- I understand that the safety and effectiveness of JUXTAPID has not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH).

### Hepatotoxicity Risk:

- I understand that there is a risk of hepatotoxicity associated with JUXTAPID.
- I understand the Recommendations for Monitoring of Transaminases with JUXTAPID treatment:

### Before treatment initiation (first dose), I must:

- Counsel patients on the approved indication for use in patients with HoFH, the risk of hepatotoxicity with JUXTAPID and the need for regular monitoring using the **Patient Guide**.
- Provide the patient a copy of the **Patient Guide**.
- Enroll the patient by completing and submitting the **Patient-Prescriber Acknowledgement Form** to the JUXTAPID REMS.

- Assess the patient to confirm a clinical or laboratory diagnosis consistent with the approved indication.
- Assess the patient's liver function.
- Order the prescription using the **Prescription Authorization Form**.

### Lab Requirements:

- I must assess liver-related tests for this patient as recommended in the JUXTAPID Prescribing Information and in the chart below.

### Monitoring of Transaminases

#### Before Initiating therapy

- Measure ALT, AST, alkaline phosphatase, and total bilirubin.

#### During the first year

- Measure liver-related tests (ALT and AST, at a minimum) **monthly** or prior to each increase in dose, whichever occurs first.

#### After the first year

- Measure liver-related tests (ALT and AST, at a minimum) at least **every 3 months** and before any increase in dose.

### During Treatment:

- I agree to complete and sign the **Prescription Authorization Form** for each prescription.
- I agree that personnel from the JUXTAPID REMS may contact me to gather further information or resolve discrepancies or to provide other information related to JUXTAPID or the JUXTAPID REMS.
- I agree that Chiesi, its agents and contractors such as the pharmacy providers may contact me via phone, mail, or email to survey me on the effectiveness of the program requirements for the JUXTAPID REMS.

A

Prescriber Signature: \_\_\_\_\_ Date: \_\_\_\_\_  
Prescriber Name: \_\_\_\_\_ Phone: \_\_\_\_\_

## IMPORTANT

## Prescription Authorization Form

**Juxtapid**  
(lomitapide) capsules



This form must be completed and signed for each JUXTAPID prescription.  
Fax this form to 1-855-898-2498.

ALL FIELDS ARE REQUIRED | PLEASE PRINT

### PATIENT INFORMATION

First Name: \_\_\_\_\_ Middle Initial: \_\_\_\_\_ Last Name: \_\_\_\_\_  
Address: \_\_\_\_\_ Phone: \_\_\_\_\_  
City: \_\_\_\_\_ Email: \_\_\_\_\_  
State: \_\_\_\_\_ Zip: \_\_\_\_\_ Date of Birth: \_\_\_\_\_

### JUXTAPID PRESCRIPTION

Dose: \_\_\_\_\_ mg po q hs (recommended starting dosage is 5 mg daily). Quantity to dispense: \_\_\_\_\_ Refills: \_\_\_\_\_  
Additional Instructions: \_\_\_\_\_

### PRESCRIBER INFORMATION

First Name: \_\_\_\_\_ Middle Initial: \_\_\_\_\_ Last Name: \_\_\_\_\_  
Practice/Facility Name: \_\_\_\_\_

B



**A**

## Complete prescriber attestation

### **Juxtapid Can Only Be Prescribed in Accordance with the FDA-Approved Indication:**

Juxtapid is indicated only 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).

**B**

## Complete the prescription and confirm dosing

Attest that patients have a diagnosis consistent with homozygous familial hypercholesterolemia (HoFH) and affirm.

### **STEP 3** Support



Once you have completed the form

### **1. Attach copies of patient insurance and prescription cards – front and back.**

### **2. First prescription for the patient:**

Fax completed form to Chiesi Total Care<sup>SM</sup> at 1-855-898-2743.

**Please complete one form per patient.**

### **3. Subsequent prescriptions:**

Each new prescription must be submitted on the REMS PAF form which may include up to 11 refills.

### **4. Let your patients know they will be receiving a call from Chiesi Total Care.**

A member of the Chiesi Total Care team will contact patients to complete and fulfill their prescriptions for Juxtapid.



**The fillable PDF can be downloaded and saved for future use.  
Scan the QR code to download a copy.**

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### CONTRAINDICATIONS:

- Pregnancy
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Reference: 1. Juxtapid® (Iomitapide) Prescribing Information. Amryt, February 2022.

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**Chiesi Total Care<sup>SM</sup> Program offered through Accredo Specialty Pharmacy.**

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Juxtapid® is a registered trademark owned by the Chiesi Group.

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PP-J-0021 V1.0 2024

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Avoid use of Juxtapid in patients with rare hereditary diseases of galactose intolerance.

### ADVERSE REACTIONS:

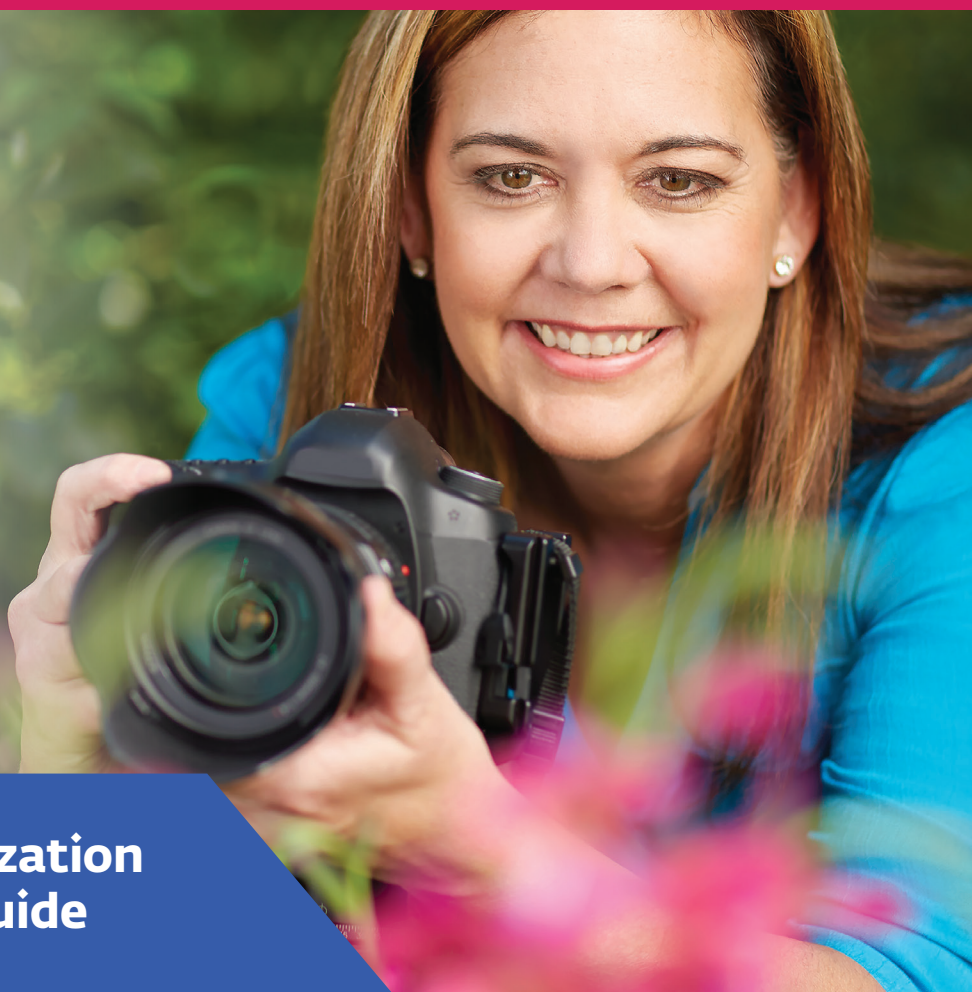
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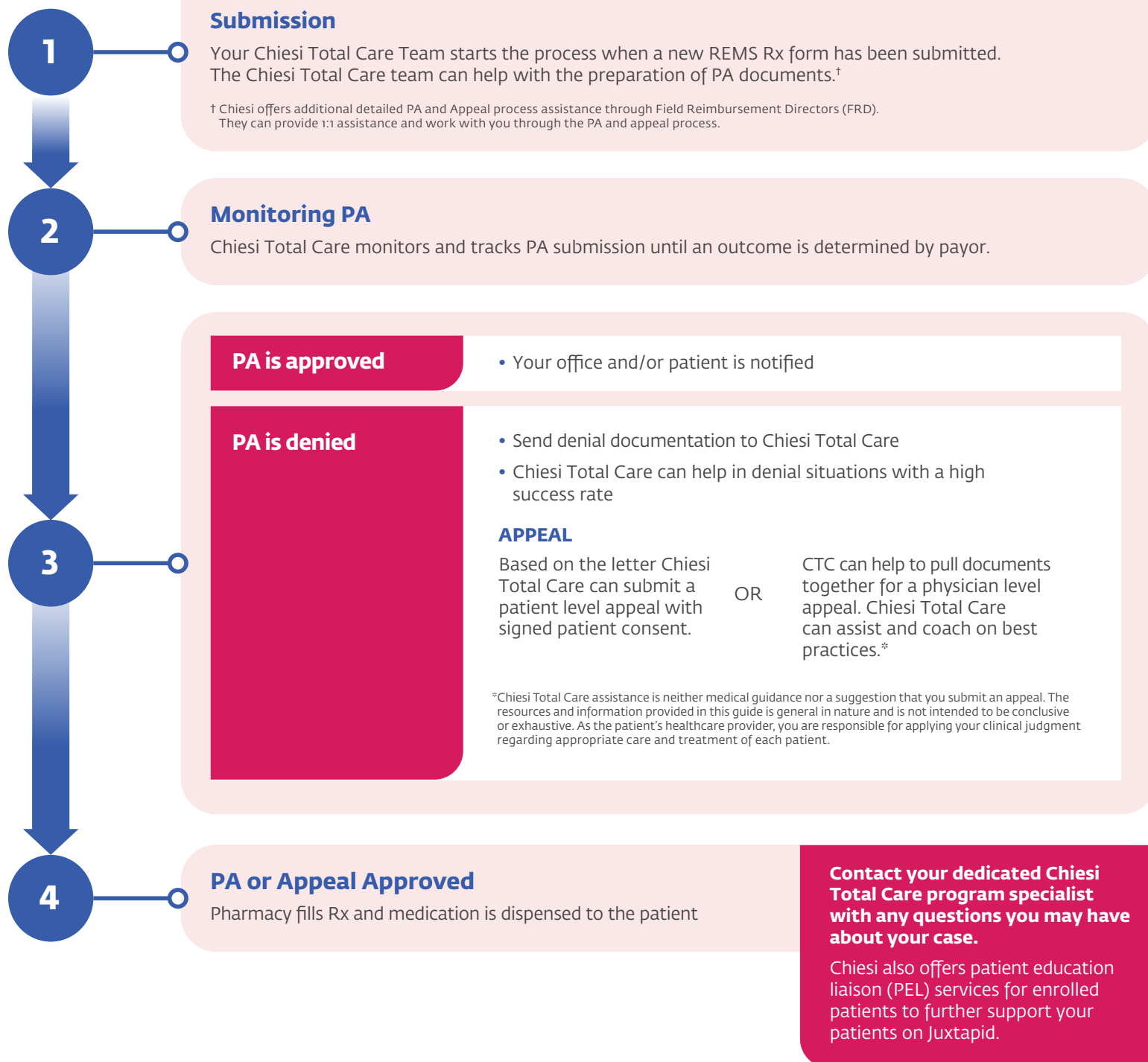
Visit [chiesitotalcare.com](http://chiesitotalcare.com) or call 1-855-898-2743. We're ready to help!





# Chiesi Total Care<sup>SM</sup> (CTC) will submit for insurance reimbursement and help you navigate prior authorization (PA).

## Here's a step-by-step look at the process



## PA denied? Chiesi Total Care is here to help.

It's not uncommon for the first PA submission to be denied. With a long track record of success in gaining PA and appeal approvals, Chiesi Total Care is here to provide assistance with the appeal process. Chiesi Total Care will assist in providing additional resources and/or publications depending on the reasons for denial. To request a copy of an additional resource or publication, please reach out directly to [us.medical@chiesi.com](mailto:us.medical@chiesi.com).

Visit [chiesitotalcare.com](https://chiesitotalcare.com) or call 1-855-898-2743. We're ready to help!

We provide updates on your patient's therapy and alert the office should there be any concerns. We also support patients by helping them cope with side effects and answering questions.



**We can help by:**

- Alerting when to refill or when refills are being missed
- Counseling patients on managing side effects
- Providing 24/7 pharmacist access
- Enrolling patients in the Juxtapid Copay Program – patients may pay as little as \$0 if eligible<sup>‡</sup>

<sup>‡</sup> Please refer to the full Terms and Conditions in the back pocket for additional eligibility requirements.

**Here is a checklist of best practices for Prior Authorization submission:**

- ☐ Include pertinent clinical notes, dates, and laboratory findings
- ☐ Include medical rationale for why the patient cannot use preferred formulary drugs
- ☐ Include prescribing practitioner NPI number and contact information
- ☐ Include therapeutic alternatives that were tried in the past

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS:**

- Pregnancy
- Concomitant administration of moderate or strong CYP3A4 inhibitors
- Moderate or severe hepatic impairment or active liver disease including unexplained persistent elevations of serum transaminases

**Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.**

## Important Safety Information about Juxtapid

### INDICATION:

Juxtapid® (Iomitapide) 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).

### LIMITATIONS OF USE:

The safety and effectiveness of Juxtapid have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH). The effect of Juxtapid on cardiovascular morbidity and mortality has not been determined.

### 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)  $\geq 3\times$  upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR), or alkaline phosphatase.**

**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.**

**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  $\geq 3\times$  ULN. Discontinue Juxtapid for clinically significant liver toxicity. 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.**

**Prescribe Juxtapid only to patients with a clinical or laboratory diagnosis consistent with HoFH. The safety and effectiveness of Juxtapid have not been established in patients with hypercholesterolemia who do not have HoFH.**

### CONTRAINDICATIONS:

- Pregnancy
- Concomitant administration of moderate or strong CYP3A4 inhibitors
- Moderate or severe hepatic impairment or active liver disease including unexplained persistent elevations of serum transaminases

### WARNINGS AND PRECAUTIONS

Juxtapid can cause elevations in transaminases and hepatic steatosis. Although cases of hepatic failure have not been reported, there is concern that Juxtapid could induce steatohepatitis, which can progress to cirrhosis over several years. Modify the dose of Juxtapid if elevations of transaminases are observed and discontinue Juxtapid for persistent or clinically significant elevations. 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  $\geq 2\times$  ULN, or active liver disease, discontinue treatment with Juxtapid and identify the probable cause. Use Juxtapid with caution when co-administered with agents known to be hepatotoxic. Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury.

Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment. 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.

Juxtapid may cause fetal harm when administered to a pregnant woman. Females of reproductive potential should have a negative pregnancy test before starting Juxtapid and should use effective contraception during therapy with Juxtapid. The recommended maximum dosage of Juxtapid is 40 mg daily when used concomitantly with oral contraceptives.

Given its mechanism of action in the small intestine, Juxtapid may reduce the absorption of fat-soluble nutrients. 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).

Gastrointestinal adverse reactions are common and may lead to treatment discontinuation. Instruct patients to stop Juxtapid and contact their healthcare provider if severe diarrhea occurs, or if they experience symptoms of volume depletion such as lightheadedness, decreased urine output, or tiredness. In such cases, consider reducing the dose or suspending use of Juxtapid. To reduce the risk of gastrointestinal adverse reactions, patients should adhere to a low-fat diet supplying less than 20% of energy from fat and the dosage of Juxtapid should be increased gradually.

Weak CYP3A4 inhibitors can increase the exposure of Iomitapide approximately 2-fold; therefore, when Juxtapid is administered with weak CYP3A4 inhibitors, the dose of Juxtapid should be decreased by half and the recommended maximum dosage of Juxtapid is 30 mg daily. The recommended maximum dosage is 40 mg daily when used concomitantly with oral contraceptives. Strong and moderate CYP3A4 inhibitors should not be used with Juxtapid. Patients taking Juxtapid 5 mg daily may continue with the same dosage.

Due to risk of myopathy associated with simvastatin or lovastatin, doses of these agents should be limited when co-administered with Juxtapid.

Juxtapid increases the plasma concentrations of warfarin. Increases or decreases in the dose of Juxtapid may lead to supra- or subtherapeutic anticoagulation, respectively. Patients taking warfarin should undergo regular monitoring of the INR, especially after any changes in Juxtapid dosage.

Avoid use of Juxtapid in patients with rare hereditary diseases of galactose intolerance.

### ADVERSE REACTIONS:

The most common adverse reactions were gastrointestinal, reported by 27 (93%) of 29 patients. Adverse reactions reported by 8 (28%) or more 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.

### REPORTING OF ADVERSE REACTIONS:

All healthcare professionals should report all suspected adverse reactions. Please contact Chiesi Farmaceutici S.p.A. at 1-888-661-9260 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.**

For more information, visit [juxtapid.com](http://juxtapid.com).

**Chiesi Total Care<sup>SM</sup> Program offered through Accredo Specialty Pharmacy.**

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PP-J-0022 V1.0 2024



**Juxtapid.**  
(Iomitapide) capsules



# Sample Letter of Appeal

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[Insurance Company]  
[Address]  
[City, State, Zip]

Re: [Patient Name]  
[Policy #]  
[DOB]  
[Address]  
[City, State, Zip]

To Whom It May Concern:

I am writing to appeal the denial of benefits for the use of [Product name (generic name)] for services requested for [Patient Name, ID#, Group #]. Included in this letter of appeal are information on the treatment rationale, medical records, medical necessity data and medical studies confirming currently prescribed product as an effective treatment for the diagnosis associated with [ICD10 Code].

**Treatment Rationale:**

[Provide information on patient response and history to past treatments and anticipated prognosis and rationale for the currently prescribed product].

**Outline of Medical Studies:**

[Outline a brief overview of the studies evaluating the use of the currently prescribed product in this condition and/or patient population. Remember to include the FDA approved indications and usage].

**Medical Record Information:**

[Highlight key dates and entries of the medical record how the currently prescribed product is used].

Per the included medical information, it is my professional opinion that the currently prescribed product is medically necessary in treating the patient and the denials for the patient's use of the drug should be reversed. Please call my office at [Office Phone Number] if I can provide further information or speak with a review board to appeal the denial of coverage decision. I look forward to reaching resolution of overturning the denied status of the currently prescribed product for this patient.

Sincerely,

[Physician Name and Signature]  
[Phone Number]

Enclosure: [Original denial notification copy]

# Sample Letter of Medical Necessity

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Use the steps above as a checklist to make sure you have completed these steps prior to sending. **It is important to follow these steps to ensure the letter is clear and concise.**



[Insurance Company]  
[Address]  
[City, State, Zip]

Re: [Patient Name]  
[Policy #]  
[DOB]  
[Address]  
[City, State, Zip]

To Whom It May Concern:

I am writing this letter of medical necessity on behalf of [Patient Name, ID#, Group #] to request coverage for [Product name (generic name)]. Included in this letter of medical necessity is information on the treatment rationale, medical records, medical necessity data and medical studies confirming currently prescribed product as an effective treatment for the diagnosis associated with [ICD10 Code].

**Treatment Rationale:**

[Provide information on patient response and history to past treatments and anticipated prognosis and rationale for the currently prescribed product].

**Outline of Medical Studies:**

[Outline a brief overview of the studies evaluating the use of the currently prescribed product in this condition and/or patient population. Remember to include the FDA approved indications and usage].

**Medical Record Information:**

[Highlight key dates and entries of the medical record how the currently prescribed product is used].

Per the included medical information, it is my professional opinion that the currently prescribed product is medically necessary in treating the patient and the denials for the patient's use of the drug should be reversed. Please call my office at [Office Phone Number] if I can provide further information.

Sincerely,

[Physician Name and Signature]  
[Phone Number]

Enclosure: [As required]



## Dosing and Administration Guide

### Important Safety Information about Juxtapid

#### INDICATION:

Juxtapid® (lomitapide) 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).

#### LIMITATIONS OF USE:

The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH). The effect of JUXTAPID on cardiovascular morbidity and mortality has not been determined.

#### 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)  $\geq 3\times$  upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR), or alkaline phosphatase.

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.

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  $\geq 3\times$  ULN. Discontinue JUXTAPID for clinically significant liver toxicity. 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.

Prescribe JUXTAPID only to patients with a clinical or laboratory diagnosis consistent with HoFH. The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.

Visit [chiesitotalcare.com](http://chiesitotalcare.com) or call 1-855-898-2743. We're ready to help!



## Convenient, Oral, Once-Daily Dosing with Juxtapid

- Juxtapid should be taken in the evening, with a glass of water, without food, and at least 2 hours after dinner.
- Prior to initiating Juxtapid treatment, measure ALT, AST, alkaline phosphate, and total bilirubin; obtain a negative pregnancy test in females of reproductive potential; and initiate a low-fat eating plan supplying less than 20% of energy from fat.



Juxtapid offers the flexibility to get patients to target dose with tolerability



AST, aspartate aminotransferase; ALT, alanine aminotransferase

### IMPORTANT SAFETY INFORMATION

#### ADVERSE REACTIONS:

The most common adverse reactions were gastrointestinal, reported by 27 (93%) of 29 patients. Adverse reactions reported by 8 (28%) or more 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.

**Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.**

### Titrate to Target Dose

- The recommended starting dosage of Juxtapid is 5 mg/day.
- Dosage should be titrated gradually based on acceptable safety and tolerability up to a maximum dosage of 60 mg/day.
- Maintenance dosing should be individualized, taking into account patient characteristics, such as target goal of therapy, response to treatment and tolerability.

### Juxtapid Dosing Titration Schedule

| Daily dosage                       | 5 mg             | 10 mg            | 20 mg            | 40 mg            | 60 mg                      |
|------------------------------------|------------------|------------------|------------------|------------------|----------------------------|
| Duration before increase in dosage | At least 2 weeks | At least 4 weeks | At least 4 weeks | At least 4 weeks | Maximum Recommended Dosage |

In the Phase 3 study, 34% of patients achieved a maximum tolerated dose of 60 mg at week 26, 24% were at 40 mg, and 21% were at 20 mg.

Monitor transaminases during treatment with Juxtapid, and reduce or withhold dosing for patients who develop transaminase values  $\geq 3\times$  ULN.

### Titrate Dose to Target

Clinical trial data and real world evidence suggest that **stepwise dose increases** are key to helping patients get closer to their LDL-C goal.

In the Phase 3 study, the **maximum tolerated doses** at week 26 by percentage of patients were 5 mg (10%), 10 mg (7%), **20 mg (21%), 40 mg (24%), and 60 mg (34%).**



Dose Escalation is Key

Visit [chiesitotalcare.com](https://chiesitotalcare.com) or call 1-855-898-2743. We're ready to help!





## Important Safety Information about Juxtapid

### INDICATION:

Juxtapid® (Iomitapide) 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).

### LIMITATIONS OF USE:

The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH). The effect of JUXTAPID on cardiovascular morbidity and mortality has not been determined.

### 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)  $\geq 3\times$  upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR), or alkaline phosphatase.**

**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.**

**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  $\geq 3\times$  ULN. Discontinue JUXTAPID for clinically significant liver toxicity. 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.**

**Prescribe JUXTAPID only to patients with a clinical or laboratory diagnosis consistent with HoFH. The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH.**

### CONTRAINDICATIONS:

- Pregnancy
- Concomitant administration of moderate or strong CYP3A4 inhibitors
- Moderate or severe hepatic impairment or active liver disease including unexplained persistent elevations of serum transaminases

### WARNINGS AND PRECAUTIONS

JUXTAPID can cause elevations in transaminases and hepatic steatosis. Although cases of hepatic failure have not been reported, there is concern that JUXTAPID could induce steatohepatitis, which can progress to cirrhosis over several years. Modify the dose of JUXTAPID if elevations of transaminases are observed and discontinue JUXTAPID for persistent or clinically significant elevations. 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  $\geq 2\times$  ULN, or active liver disease, discontinue treatment with JUXTAPID and identify the probable cause. Use JUXTAPID with caution when co-administered with agents known to be hepatotoxic. Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury.

Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment. 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.

JUXTAPID may cause fetal harm when administered to a pregnant woman. Females of reproductive potential should have a negative pregnancy test before starting JUXTAPID and should use effective contraception during therapy with JUXTAPID. The recommended maximum dosage of JUXTAPID is 40 mg daily when used concomitantly with oral contraceptives.

Given its mechanism of action in the small intestine, JUXTAPID may reduce the absorption of fat-soluble nutrients. 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).

Gastrointestinal adverse reactions are common and may lead to treatment discontinuation. Instruct patients to stop JUXTAPID and contact their healthcare provider if severe diarrhea occurs, or if they experience symptoms of volume depletion such as lightheadedness, decreased urine output, or tiredness. In such cases, consider reducing the dose or suspending use of JUXTAPID. To reduce the risk of gastrointestinal adverse reactions, patients should adhere to a low-fat diet supplying less than 20% of energy from fat and the dosage of JUXTAPID should be increased gradually.

Weak CYP3A4 inhibitors can increase the exposure of Iomitapide approximately 2-fold; therefore, when JUXTAPID is administered with weak CYP3A4 inhibitors, the dose of JUXTAPID should be decreased by half and the recommended maximum dosage of JUXTAPID is 30 mg daily. The recommended maximum dosage is 40 mg daily when used concomitantly with oral contraceptives. Strong and moderate CYP3A4 inhibitors should not be used with JUXTAPID. Patients taking JUXTAPID 5 mg daily may continue with the same dosage.

Due to risk of myopathy associated with simvastatin or lovastatin, doses of these agents should be limited when co-administered with JUXTAPID.

JUXTAPID increases the plasma concentrations of warfarin. Increases or decreases in the dose of JUXTAPID may lead to supra- or subtherapeutic anticoagulation, respectively. Patients taking warfarin should undergo regular monitoring of the INR, especially after any changes in JUXTAPID dosage.

Avoid use of JUXTAPID in patients with rare hereditary diseases of galactose intolerance.

### ADVERSE REACTIONS:

The most common adverse reactions were gastrointestinal, reported by 27 (93%) of 29 patients. Adverse reactions reported by 8 (28%) or more 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.

### REPORTING OF ADVERSE REACTIONS:

All healthcare professionals should report all suspected adverse reactions. Please contact Chiesi Farmaceutici S.p.A. at 1-888-661-9260 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.**

For more information, visit [juxtapid.com](http://juxtapid.com).

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PP-J-0023 V1.0 2024





**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). Prescribe JUXTAPID only to patients with a clinical or laboratory diagnosis consistent with HoFH. The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH (1).

**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, including those with heterozygous familial hypercholesterolemia (HeFH) (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, 20 mg, and 30 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: May cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception. Discontinue JUXTAPID if pregnancy detected (5.3, 8.1, 8.3).
- 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 Chiesi Farmaceutici S.p.A. at 1-888-661-9260 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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 (4, 5.6, 7.1).
- When administered with weak CYP3A4 inhibitors, the dose of JUXTAPID should be decreased by half. The dosage of JUXTAPID may then be up-titrated to a maximum recommended dosage of 30 mg daily (2.3, 5.6, 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**

- Lactation: Breastfeeding not recommended (8.2).
- Pediatric Patients: Safety and effectiveness not established (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2024

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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)  $\geq 3$ x 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  $\geq 3$ x 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 \(5.2\)](#)]. Prescribe JUXTAPID only to patients with a clinical or laboratory diagnosis consistent with HoFH. The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH [see [Indications and Usage \(1\)](#)].**

## 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, including those with heterozygous familial hypercholesterolemia (HeFH).

- 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 prior to initiating treatment with JUXTAPID [*see Contraindications (4), Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)*];
- 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 weak CYP3A4 inhibitors and for those with renal impairment or baseline hepatic impairment [*see Dosage and Administration (2.3), (2.5), and (2.6)*]. Monitor transaminases during treatment with JUXTAPID as described in *Warnings and Precautions (5.1)*, and reduce or withhold dosing for patients who develop transaminase values  $\geq 3$ x the upper limit of normal (ULN) [*see Dosage and Administration (2.4)*].

**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, pazopanib, ranitidine, ranolazine, ticagrelor, zileuton). However, the recommended maximum dosage of JUXTAPID is 40 mg daily with concomitant use of oral contraceptives.

When initiating a weak CYP3A4 inhibitor in a patient already taking JUXTAPID 10 mg daily or more, decrease the dose of JUXTAPID by half; patients taking JUXTAPID 5 mg daily may continue with the same dosage. Careful titration of JUXTAPID may then be considered according to LDL-C response and safety/tolerability to a maximum recommended dosage of 30 mg daily except when coadministered with oral contraceptives, in which case the maximum recommended lomitapide dosage is 40 mg daily [see *Drug Interactions (7.2)*].

## 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 | <ul style="list-style-type: none"><li>• Confirm elevation with a repeat measurement within one week.</li><li>• If confirmed, reduce the dose and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR).</li><li>• 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.</li><li>• If resuming JUXTAPID after transaminases resolve to &lt;3x ULN, consider reducing the dose and monitor liver-related tests more frequently.</li></ul> |
| ≥5x ULN         | <ul style="list-style-type: none"><li>• 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.</li><li>• If resuming JUXTAPID after transaminases resolve to &lt;3x ULN, reduce the dose and monitor liver-related tests more frequently.</li></ul>   |

\*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 \(8.6\)](#)].

## 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 \(8.7\)](#)].

### 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”

30 mg: Orange/yellow hard gelatin capsule printed with black ink “A733” and “30 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 Specific Populations (8.7)*].

### 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  $\geq 3$ x ULN, and 4 (14%) of the patients had at least one elevation in ALT or AST  $\geq 5$ x ULN. There were no concomitant or subsequent clinically meaningful elevations in bilirubin, INR, or alkaline phosphatase [see *Adverse Reactions (6.1)*].

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)*].

### Monitoring of Transaminases

Before initiating JUXTAPID and during treatment, monitor transaminases as recommended in Table 3.

**Table 3: Recommendations for Monitoring Transaminases**

| TIME                         | RECOMMENDATIONS  |
|------------------------------|--|
| Before initiating treatment  | <ul style="list-style-type: none"> <li>• Measure ALT, AST, alkaline phosphatase, and total bilirubin.</li> <li>• If abnormal, consider initiating JUXTAPID only after an appropriate work-up and the baseline abnormalities have been explained or resolved.</li> <li>• JUXTAPID is contraindicated in patients with moderate or severe hepatic impairment, or active liver disease, including unexplained persistent elevations of serum transaminases [<i>see Contraindications (4)</i>].</li> </ul>   |
| During the first year        | <ul style="list-style-type: none"> <li>• Measure liver-related tests (ALT and AST, at a minimum) prior to each increase in dose or monthly, whichever occurs first.</li> </ul>   |
| After the first year         | <ul style="list-style-type: none"> <li>• Measure liver-related tests (ALT and AST, at a minimum) at least every 3 months and before any increase in dose.</li> </ul>   |
| At any time during treatment | <ul style="list-style-type: none"> <li>• If transaminases are abnormal, reduce or withhold dosing of JUXTAPID and monitor as recommended [<i>see Dosage and Administration (2.4)</i>].</li> <li>• Discontinue JUXTAPID for persistent or clinically significant elevations.</li> <li>• 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 <math>\geq 2</math>x ULN, or active liver disease, discontinue treatment with JUXTAPID and identify the probable cause.</li> </ul> |

### 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.

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  $\geq 3$  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.

JUXTAPID has not been studied concomitantly with other LDL-lowering agents that can also increase hepatic fat. Therefore, the combined use of such agents is not recommended.

## **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](http://www.JUXTAPIDREMSProgram.com) or by telephone at 1-855-JUXTAPID (1-855-898-2743).

## **5.3 Embryo-Fetal Toxicity**

Based on findings from animal studies, JUXTAPID use is contraindicated in pregnancy since it may cause fetal harm [see *Contraindications (4)*, *Use in Specific Populations (8.1, 8.3)*]. In animal reproduction studies in rats and ferrets, embryonic death and fetal malformations were observed at clinically relevant exposures. Females of reproductive potential should have a negative pregnancy test before starting JUXTAPID. Advise females of reproductive potential to use effective contraception during therapy with JUXTAPID and for two weeks after the final dose. If pregnancy is detected, discontinue JUXTAPID.

#### **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 \(2.1\)](#)]. 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.

There have been postmarketing reports of severe diarrhea with the use of JUXTAPID, including patients being hospitalized because of diarrhea-related complications such as volume depletion. Monitor patients who are more susceptible to complications from diarrhea, such as older patients and patients taking drugs that can lead to volume depletion or hypotension. Instruct patients to stop JUXTAPID and contact their healthcare provider if severe diarrhea occurs or if they experience symptoms of volume depletion such as lightheadedness, decreased urine output, or tiredness. In such cases, consider reducing the dose or suspending use of JUXTAPID.

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 lomitapide, 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 can increase the exposure of lomitapide approximately 2-fold; therefore, when JUXTAPID is administered with weak CYP3A4 inhibitors, the dose of JUXTAPID should be decreased by half. Careful titration may then be considered based on LDL-C response and safety/tolerability to a maximum recommended dosage of 30 mg daily except when coadministered with oral contraceptives, in which case the maximum recommended lomitapide dosage is 40 mg daily [see [Dosage and Administration \(2.3\)](#) and [Drug Interactions \(7.2\)](#)].

### **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 \(5.5\)](#)]

### **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  $\geq 8$  (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 4.

**Table 4: Adverse Reactions Reported in  $\geq 10\%$  of Patients in the Clinical Trial in HoFH**

| ADVERSE REACTION                  | N (%)   |
|-----------------------------------|---------|
| <i>Gastrointestinal Disorders</i> |         |
| 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)  |
| <i>Infections</i>                 |         |
| Influenza                         | 6 (21)  |
| Nasopharyngitis                   | 5 (17)  |
| Gastroenteritis                   | 4 (14)  |
| <i>Investigations</i>             |         |
| Decreased weight                  | 7 (24)  |
| Increased ALT                     | 5 (17)  |
| <i>General Disorders</i>          |         |
| Chest pain                        | 7 (24)  |
| Fatigue                           | 5 (17)  |

| ADVERSE REACTION                 | N (%)  |
|----------------------------------|--------|
| Fever                            | 3 (10) |
| <i>Musculoskeletal Disorders</i> |        |
| Back pain                        | 4 (14) |
| <i>Nervous System Disorders</i>  |        |
| Headache                         | 3 (10) |
| Dizziness                        | 3 (10) |
| <i>Respiratory Disorders</i>     |        |
| Pharyngolaryngeal pain           | 4 (14) |
| Nasal congestion                 | 3 (10) |
| <i>Cardiac Disorders</i>         |        |
| Angina pectoris                  | 3 (10) |
| Palpitations                     | 3 (10) |

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  $\geq 3$ x ULN (see Table 5). 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 5: Patient Incidence of Transaminase Elevations During the HoFH Clinical Trial**

|                          | N (%)   |
|--------------------------|---------|
| <b>Total Patients</b>    | 29      |
| <b>Maximum ALT</b>       |         |
| $\geq 3$ to $<5$ x ULN   | 6 (21%) |
| $\geq 5$ to $<10$ x ULN  | 3 (10%) |
| $\geq 10$ to $<20$ x ULN | 1 (3%)  |
| $\geq 20$ x ULN          | 0       |
| <b>Maximum AST</b>       |         |
| $\geq 3$ to $<5$ x ULN   | 5 (17%) |
| $\geq 5$ to $<10$ x ULN  | 1 (3%)  |
| $\geq 10$ to $<20$ x ULN | 0       |

|           |   |
|-----------|---|
| ≥20 x 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 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.

## **6.2 Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of JUXTAPID. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to JUXTAPID exposure.

*Musculoskeletal disorders:* Myalgia

*Skin reactions:* Alopecia

## **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, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, 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 (such as alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, lapatinib, nilotinib, pazopanib, ranitidine, ranolazine, ticagrelor, zileuton) can increase lomitapide exposure approximately 2-fold [see *Clinical Pharmacology* (12.3)]. When administered with weak CYP3A4 inhibitors, the dose of JUXTAPID should be decreased by half. Careful titration of JUXTAPID may then be considered based on LDL-C response and safety/tolerability to a maximum recommended dosage of 30 mg daily except when coadministered with oral contraceptives, in which case the maximum recommended lomitapide dosage is 40 mg daily [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 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 Exposure Registry***

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to JUXTAPID during pregnancy. For additional information visit [www.JUXTAPID.com](http://www.JUXTAPID.com) or call the Global Lomitapide Pregnancy Exposure Registry (PER) at 1-877-902-4099. Healthcare professionals are encouraged to call the PER at 1-877-902-4099 to enroll patients who become pregnant during JUXTAPID treatment.

#### ***Risk Summary***

Based on findings from animal studies, JUXTAPID use is contraindicated in pregnancy since it may cause fetal harm [see [Contraindications \(4\)](#), [Warnings and Precautions \(5.3\)](#)]. Available human data are insufficient to draw conclusions about any drug-associated risks for major birth



defects, miscarriage, or adverse maternal or fetal outcomes. However, in animal reproduction studies, lomitapide was teratogenic in rats at clinically relevant exposures and in ferrets at exposures estimated to be less than human therapeutic exposure at 60 mg when administered during organogenesis, based on AUC comparisons. Embryo-fetal lethality was observed in rabbits at 6-times the maximum recommended human dose (MRHD) of 60 mg based on body surface area. If pregnancy is detected, discontinue JUXTAPID.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

## ***Data***

### *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  $\geq 2$ -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  $\geq 20$  mg/kg/day,  $\geq 6$ -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.

## **8.2 Lactation**

### ***Risk Summary***

There are no data on the presence of lomitapide in human or animal milk, effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions, including hepatotoxicity, advise patients that breastfeeding is not recommended during treatment with JUXTAPID.

## **8.3 Females and Males of Reproductive Potential**

### ***Pregnancy Testing***

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

### ***Contraception***

Based on animal studies, JUXTAPID may cause fetal harm when administered to pregnant women [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with JUXTAPID and for two weeks after the final dose.

The use of JUXTAPID may result in reduced efficacy of oral contraceptives if vomiting or diarrhea occurs. Advise patients using oral contraceptives and who experience vomiting or diarrhea to use an effective alternative contraceptive method until 7 days after resolution of symptoms [*see Drug Interactions (7.2)*].

## **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 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 \(12.3\)](#)].

## 8.7 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 \(12.3\)](#)].

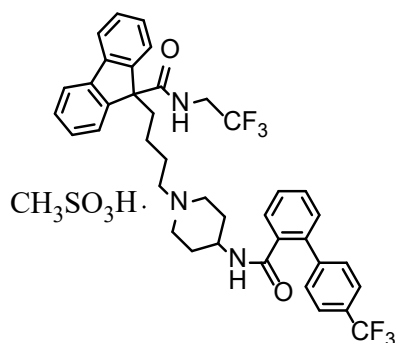
## 10 OVERDOSAGE

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]-9H-fluorene-9-carboxamide, methanesulfonate salt. Its structural formula is:



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, 20, or 30 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 of all strengths contain gelatin and titanium dioxide; the 5 mg, 10 mg and 30 mg capsules also contain red iron oxide; and the 30 mg capsules also contain yellow 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.

## 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, 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* (8.7)].

#### *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  $AUC_{0-\infty}$  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* (8.6)].

#### **Drug Interactions**

[see *Dosage and Administration* (2.3), *Contraindications* (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 6 summarizes the effect of coadministered drugs on lomitapide AUC and  $C_{\max}$ .

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

| COADMINISTERED<br>DRUG  | DOSING OF<br>COADMINISTERED<br>DRUG        | DOSING OF<br>LOMITAPIDE | RATIO OF LOMITAPIDE EXPOSURE WITH/WITHOUT<br>COADMINISTERED DRUG<br>No Effect = 1 |                  |
|---|--|-------------------------|---|------------------|
|   |  |                         | AUC   | C <sub>max</sub> |
| Contraindicated with lomitapide [see <i>Contraindications (4)</i> and <i>Warnings and Precautions (5.6)</i> ]                                       |  |                         |   |                  |
| Ketoconazole  | 200 mg BID for<br>9 days                   | 60 mg single<br>dose    | ↑ 27  | ↑ 15             |
| Adjustment necessary when coadministered with lomitapide [see <i>Dosage and Administration (2.3)</i><br>and <i>Warnings and Precautions (5.6)</i> ] |  |                         |   |                  |
|   |  |                         | AUC   | C <sub>max</sub> |
| Atorvastatin  | 80 mg QD                                   | 20 mg single<br>dose    | ↑2  | ↑2.1             |
| Ethinyl Estradiol<br>(EE) / norgestimate  | 0.035 mg EE/<br>0.25 mg<br>norgestimate QD | 20 mg single<br>dose    | ↑1.3  | ↑1.4             |

BID = twice daily; QD = once daily

↑ = increase

### *Effect of Lomitapide on other Drugs*

Table 7 summarizes the effects of lomitapide on the AUC and C<sub>max</sub> of coadministered drugs.

**Table 7: Effect of Lomitapide on the Systemic Exposure of Coadministered Drugs**

| COADMINISTERED<br>DRUG  | DOSING OF<br>COADMINISTERED<br>DRUG    | DOSING OF<br>LOMITAPIDE                | CHANGE OF COADMINISTERED DRUG<br>EXPOSURE WITH / WITHOUT<br>LOMITAPIDE |                              |                               |
|---|--|--|--|------------------------------|-------------------------------|
|   |  |  |  | AUC                          | C <sub>max</sub>              |
| Dosage adjustment necessary when coadministered with lomitapide |  |  |  |                              |                               |
| Simvastatin <sup>a</sup>  | 40 mg single dose                      | 60 mg QD × 7 days                      | Simvastatin<br>Simvastatin acid  | ↑ 99%<br>↑ 71%               | ↑ 102%<br>↑ 57%               |
|   | 20 mg single dose                      | 10 mg QD x 7 days                      | Simvastatin<br>Simvastatin acid  | ↑ 62%<br>↑ 39%               | ↑ 65%<br>↑ 35%                |
| Warfarin <sup>b</sup>   | 10 mg single dose                      | 60 mg QD x 12 days                     | R(+) warfarin<br>S(-) warfarin<br>INR                                  | ↑ 28%<br>↑ 30%<br>↑ 7%       | ↑ 14%<br>↑ 15%<br>↑ 22%       |
| No dosing adjustments required for the following:               |  |  |  |                              |                               |
| Atorvastatin  | 20 mg single dose<br>20 mg single dose | 60 mg QD × 7 days<br>10 mg QD × 7 days | Atorvastatin<br>acid<br>Atorvastatin<br>acid                           | ↑ 52%<br>↑ 11%               | ↑ 63%<br>↑ 19%                |
|   | Rosuvastatin                           | 20 mg single dose<br>20 mg single dose | 60 mg QD × 7 days<br>10 mg QD × 7 days                                 | Rosuvastatin<br>Rosuvastatin | ↑ 32%<br>↑ 2%<br>↑ 4%<br>↑ 6% |
| Fenofibrate, micronized   | 145 mg single dose                     | 10 mg QD × 7 days                      | Fenofibric acid  | ↓ 10%                        | ↓ 29%                         |
| Ezetimibe   | 10 mg single dose                      | 10 mg QD × 7 days                      | Total<br>ezetimibe   | ↑ 6%                         | ↑ 3%                          |
| Extended release niacin   | 1000 mg single<br>dose                 | 10 mg QD × 7 days                      | Nicotinic acid   | ↑ 10%                        | ↑ 11%                         |
|   |  |  | Nicotinuric acid   | ↓ 21%                        | ↓ 15%                         |
| Ethinyl estradiol   | 0.035 mg QD x 28<br>days               | 50 mg QD x 8 days                      | Ethinyl estradiol  | ↓ 8%                         | ↓ 8%                          |
| Norgestimate  | 0.25 mg QD x 28<br>days                | 50 mg QD x 8 days                      | 17-Deacetyl<br>norgestimate  | ↑ 6%                         | ↑ 2%                          |

<sup>a</sup> 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.

<sup>b</sup> 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  $\geq 1.5$  mg/kg/day ( $\geq 2$ -times the MRHD at 60 mg based on AUC) and in females at  $\geq 7.5$  mg/kg/day ( $\geq 10$ -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  $\geq 15$  mg/kg/day ( $\geq 23$ -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.

## 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  $25.8 \text{ kg/m}^2$ , 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.

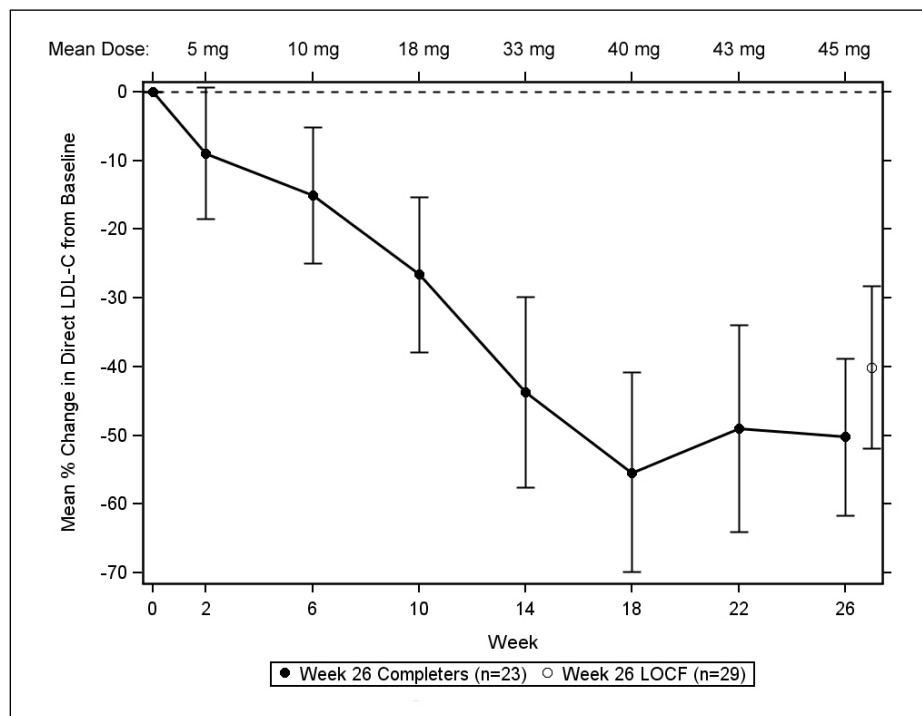
After a six-week run-in period to stabilize lipid-lowering treatments, including the establishment of an LDL apheresis schedule if applicable, JUXTAPID was initiated at 5 mg daily and titrated to daily doses of 10 mg, 20 mg, 40 mg, and 60 mg at weeks 2, 6, 10, and 14, respectively, based

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 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.

Changes in lipids and lipoproteins through the efficacy endpoint at Week 26 are presented in Table 8.

**Table 8: 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) <sup>a</sup> | 92 [72, 128] | 57 [36, 78]         | -45 *         |
| HDL-C (mg/dL)           | 44 (11)      | 41 (13)             | -7            |

<sup>a</sup> 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 10122-405-28

### *10 mg capsules:*

Orange/white hard gelatin capsule printed with black ink “A733” and “10 mg”

Bottles of 28

NDC 10122-410-28

### *20 mg capsules:*

White/white hard gelatin capsule printed with black ink “A733” and “20 mg”

Bottles of 28

NDC 10122-420-28

### *30 mg capsules:*

Orange/yellow hard gelatin capsule printed with black ink “A733” and “30 mg”

Bottles of 28

NDC 10122-430-28

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.

## 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](http://www.JUXTAPID.com) or call 1-877-902-4099.

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.

### Embryofetal Toxicity [see [Warnings and Precautions \(5.3\)](#), [Drug Interactions \(7.2\)](#), [Use in Specific Populations \(8.1, 8.3\)](#)]

- JUXTAPID is contraindicated in pregnancy since it may cause fetal harm. Advise females who become pregnant to discontinue JUXTAPID and inform their healthcare provider of a known or suspected pregnancy.
- Advise females of reproductive potential to use effective contraception during treatment with JUXTAPID and for two weeks after the final dose.

- Advise patients who are taking oral contraceptives and experience vomiting or diarrhea while taking JUXTAPID to use an effective alternative contraceptive method until 7 days after resolution of symptoms.

#### Lactation [see [Use in Specific Populations \(8.2\)](#)]

Advise females not to breastfeed during treatment with 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).

#### 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.
- Instruct the patient to stop JUXTAPID and contact their healthcare provider if severe diarrhea occurs or if they experience symptoms of volume depletion such as lightheadedness, decreased urine output, or tiredness.
- 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.

Manufactured for:  
Chiesi Farmaceutici S.p.A.  
43122 Parma, Italy

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**Medication Guide**  
**JUXTAPID® (JUKS-tuh-pid)**  
(lomitapide)  
capsules

**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](http://www.JUXTAPID.com) or call 1-877-902-4099.

**JUXTAPID may cause serious side effects including:**

**1. Liver problems.** JUXTAPID can cause liver problems such as increased liver enzymes or increased fat in the liver.

- 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
  - flu-like symptoms
  - yellowing of your eyes or skin
  - you are more tired than usual
- 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.
  - 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.
  - Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors outcomes in women exposed to JUXTAPID during pregnancy. If you become pregnant while taking JUXTAPID, call 1-877-902-4099 or visit [www.JUXTAPID.com](http://www.JUXTAPID.com) for more information about the JUXTAPID pregnancy exposure registry.

**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 and effective in people with high cholesterol who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH).

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.

**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 over-the-counter 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 colestevlam 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 colestevlam 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.
- 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:**

- See **“What is the most important information I should know about JUXTAPID?”**
- **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?”**

- **gastrointestinal symptoms.** Diarrhea, nausea, vomiting, and stomach pain or discomfort are very common when taking JUXTAPID. Strictly following a low-fat diet may help lower the chance of having these symptoms. Stop taking Juxtapid and tell your doctor if you have severe diarrhea, especially if you also have lightheadedness, decreased urine output, or tiredness.
- **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
- nausea
- vomiting
- indigestion
- stomach cramping/pain

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.
- 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](http://www.JUXTAPID.com) or call 1-85-JUXTAPID (1-855-898-2743).

**What are the ingredients in JUXTAPID?**

**Active ingredient:** lomitapide mesylate

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

**Capsule shell:** The capsule shells of all strengths contain gelatin and titanium dioxide; the 5 mg, 10 mg and 30 mg capsules also contain red iron oxide; and the 30 mg capsules also contain yellow iron oxide. The imprinting ink contains shellac, black iron oxide, and propylene glycol.



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Manufactured for: Chiesi Farmaceutici S.p.A., Parma, Italy.

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

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# Juxtapid® Chiesi Total Care™ Patient Support Services Program Terms and Conditions

To enroll in Chiesi Total Care (the "Program") and to assess eligibility for patient support services of the Program, patient must complete the Program Enrollment and Authorization Form and have a valid prescription for an eligible product of the Program. Additional documentation may be required. The patient must be a resident of the United States or one of its territories. If the patient is incapable of acting on their own behalf or if the patient is under 18 years old, enrollment into the Program may be completed by another person acting on their behalf (such as a caregiver).

A patient who receives healthcare benefits under any plan or program funded in whole or in part by federal or state governments including Medicare, Medicaid, TRICARE, Veterans Affairs (VA), State Prescription Assistance Plans (SPAPs) (other than health insurance for federal government employees), or any state healthcare program such as Medicaid, Children's Health Insurance Program, programs funded under Maternal and Child Health Program, or programs funded under Social Services Block Grant (collectively, "Government-funded Plans") are not eligible for the financial patient support services of the Program. A patient covered under a commercial health plan purchased through a health insurance marketplace or exchange is not a government-funded Plan beneficiary even if the costs of such coverage are subsidized by the federal government. If a change in prescription drug coverage should occur, the patient must notify the Program; such change may affect eligibility for the support services provided in the Program. Patients who have been prescribed a product for an indication that is not consistent with the US Food and Drug Administration-approved labeling will not be eligible for financial patient support services offered through the Program.

Patients residing in or receiving treatment in certain states may not be eligible for certain patient support services of the Program. Patients may not seek reimbursement for value received from the Program. The Program does not obligate the use of any specific medication or healthcare provider. Patients who receive treatment or reside in Massachusetts, Michigan, Minnesota, or Rhode Island are not eligible for co-pay assistance for infusion services or routine testing services.

Chiesi Total Care may recommend contacting an independent financial assistance foundation. Independent financial assistance foundations have their own rules for eligibility. Chiesi USA does not fund independent financial assistance foundations, nor does Chiesi Total Care have involvement or influence in independent foundation decision making or eligibility criteria and does not know if a foundation will be able to help you. Chiesi Total Care can only refer you to a foundation that supports your disease state. This information is provided as a resource for you. Chiesi Total Care does not endorse or show preference for any foundation. The foundations recommended to you may not be the only ones that might be able to help you.

Chiesi Patient Education Liaisons ("PELs") may be available to assist you with disease education, provide relative educational or informational resources, and to answer questions you may have about your disease. Chiesi Field Reimbursement Managers ("FRMs") may be available to assist you with your product prescription drug coverage, including prior authorization, appeals, and denials.

PELs and FRMs are employees of Chiesi USA, Inc. PELs and FRMs are not healthcare providers and are not part of your healthcare team. PELs or FRMs will not provide medical care or advice. All treatment decisions should be made by you and your treating healthcare professional. To assist you, PELs and FRMs may need your Information. If you choose to opt out of services by PELs and FRMs, you may do so at any time. Please see Chiesi's Privacy Policy at [www.chiesiusa.com/privacy](http://www.chiesiusa.com/privacy).

Program benefits may not be sold, purchased, traded, or offered for sale, purchase, or trade. The Chiesi Total Care patient support services are not valid where prohibited by law, taxed, or otherwise restricted. Offer subject to change or discontinuance without notice. Restrictions, including monthly maximums, may apply. This is not health insurance.

This is a voluntary program. Patients who choose not to enroll in the Program will be able to receive medication. Patients may participate in Chiesi Total Care without participating in a patient support services program of Chiesi Total Care. After enrolling in Chiesi Total Care, participants may opt out by contacting the Program, as outlined in the Chiesi Total Care Enrollment and Authorization Form. Patients must renew their eligibility by December 31 of each year to continue to receive support under the Program.

By participating in the Program, participants acknowledge that they understand and agree to comply with the Program Terms and Conditions.

## Important Safety Information

### Indication

Juxtapid is a prescription medicine used along with diet and other lipid lowering treatments, including low-density lipoprotein (LDL) apheresis where available, in adults with homozygous familial hypercholesterolemia (HoFH) to reduce LDL ("bad") cholesterol, total cholesterol, a protein that carries bad cholesterol in the blood (apolipoprotein B), and non-high-density lipoprotein cholesterol (non-HDL-C).

Studies have not been conducted to tell us whether Juxtapid can help prevent problems from high cholesterol, such as heart attack, stroke, death, or other health problems. Studies have also not been conducted to tell us whether Juxtapid is safe for use in people with high cholesterol who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH).

### Juxtapid may cause serious side effects, including:

#### Liver Problems

- Juxtapid can cause liver problems such as increased liver enzymes or increased fat in the liver. For this reason, your doctor should do blood tests to check your liver before you start Juxtapid and while you are taking Juxtapid (especially if your dose is increased). If your tests show signs of liver problems, your doctor may lower your dose of Juxtapid or stop it altogether.
- You should tell your doctor if you have had liver problems in the past, including liver problems while taking other medicines.
- Stomach problems can also be a symptom of liver problems. Tell your doctor right away if you have nausea; vomiting or stomach pain that gets worse, does not go away, or changes; fever; yellowing of your eyes or skin; feeling more tired than usual; or having flu-like symptoms while taking Juxtapid because these may be signs of liver problems.
- Do not drink more than 1 alcoholic drink per day while taking Juxtapid.

#### Harm to your unborn baby:

- Do not take Juxtapid if you are pregnant, think you may be pregnant, or are planning to become pregnant.
- You should have a negative pregnancy test result before you can start on Juxtapid. Use effective birth control while taking Juxtapid. If you become pregnant while taking Juxtapid, stop taking Juxtapid and call your doctor right away.

#### You should not take Juxtapid if you:

- Are taking medications known as moderate or strong CYP3A4 inhibitors (for example, certain medications used to treat bacterial, fungal, or viral infections, as well as certain medications used to treat depression, high blood pressure, or angina). These medications may affect how your body breaks down Juxtapid.
- Have moderate to severe liver problems or active liver disease, including abnormal liver function tests.

#### Other possible side effects of Juxtapid:

- The most common side effects of Juxtapid are stomach problems including diarrhea, nausea, vomiting, cramps/pain, indigestion, and/or gas. You may be able to reduce your chance of stomach problems by following an eating plan consisting of less than 20% of calories from fat.
- Juxtapid makes it harder for some fat-soluble nutrients, such as vitamin E and fatty acids, to get into your body. Take supplements that contain fat-soluble vitamins each day while you take Juxtapid. Ask your doctor, nurse, or dietitian how to take them.

Tell your doctor if you have any side effect that bothers you or that does not go away. Stop taking Juxtapid and tell your doctor if you have severe diarrhea, especially if you also have lightheadedness, decreased urine output, or tiredness. These are not all the possible side effects of Juxtapid. For more information, speak with your doctor or pharmacist.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Juxtapid may affect the way other medicines work, and other medicines may affect how Juxtapid works.

**You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.FDA.gov/medwatch](http://www.FDA.gov/medwatch) or call 1-800-FDA-1088.**

**This is the most important information about Juxtapid. For more detailed information, Please see the Medication Guide and full Prescribing Information including Box Warning.**



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