PRODUCT MONOGRAPH

Pr JUXTAPID™

lomitapide capsules

5 mg, 10 mg and 20 mg lomitapide (as lomitapide mesylate)

Microsomal Triglyceride Transfer Protein Inhibitor

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JUXTAPID™

lomitapide capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Capsule 5 mg , 10 mg, 20 mg	Gelatin, lactose white monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, red iron oxide (5 mg and 10 mg only), silicon dioxide, sodium starch glycolate, titanium dioxide.

INDICATIONS AND CLINICAL USE

JUXTAPID™ (lomitapide) is indicated as an adjunct to a low-fat diet and other lipid-lowering drugs, with or without LDL apheresis, to reduce low-density lipoprotein cholesterol (LDL-C) in adult patients with homozygous familial hypercholesterolemia (HoFH).

Due to its benefit-risk profile, the prescribing of JUXTAPID should be limited to physicians experienced in the diagnosis and treatment of familial hypercholesterolemia.

The effect of JUXTAPID on cardiovascular morbidity and mortality has not been determined.

Geriatrics (≥ 65 years of age)

Clinical studies of JUXTAPID did not include sufficient numbers of patients with HoFH aged 65 years and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients.

Pediatrics (< 18 years)

The safety and effectiveness in pediatric patients have not been established.

CONTRAINDICATIONS

- Patients with moderate or severe hepatic impairment, including those with unexplained persistent abnormal liver function tests (see WARNINGS AND PRECAUTIONS, Risk of Hepatotoxicity)

- Patients with a known significant, chronic bowel disease, such as inflammatory bowel disease or malabsorption (see DOSAGE AND ADMINISTRATION)

- Concomitant administration of >20 mg daily simvastatin (40 mg daily is allowed for patients who have previously tolerated simvastatin 80 mg daily for at least one year without evidence of muscle toxicity) (see DRUG INTERACTIONS, Drug-Drug Interactions)

- Concomitant use of JUXTAPID (lomitapide) with strong or moderate CYP 3A4 inhibitors, e.g., antifungal azoles, such as itraconazole, fluconazole, or ketoconazole; macrolide antibiotics, such as erythromycin, or clarithromycin; ketolide antibiotics, such as telithromycin; HIV protease inhibitors such as indinavir, nelfinavir, tipranavir/ritonavir, saquinavir; calcium channel blockers, such as diltiazem or verapamil; the antidepressant, nefazodone; or, the anti-arrhythmic, dronedarone (see DRUG INTERACTIONS, Drug-Drug Interactions)

- Pregnancy (see WARNINGS AND PRECAUTIONS, Pregnant Women)

- Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency, or glucose-galactose malabsorption

- Patients who are hypersensitive to JUXTAPID, or to any ingredient in the formulation or component of the container. For a complete listing, see PHARMACEUTICAL INFORMATION, Drug Substance, *Physicochemical Properties*.

WARNINGS AND PRECAUTIONS

Risk of Hepatotoxicity

Hepatic Steatosis

Consistent with the mechanism of action of JUXTAPID (lomitapide), most treated patients exhibited increases in hepatic triglyceride content, with or without concomitant increases in hepatic transaminases. In an open-label Phase 3 study, 18 of 23 patients with HoFH developed hepatic steatosis, i.e., hepatic fat > 5.6%, as measured by nuclear magnetic resonance spectroscopy (NMRS). There was a mean increase in absolute hepatic fat content of 6% after

both 26 weeks and 78 weeks of treatment, from a mean of 1% at baseline (see ADVERSE REACTIONS). Clinical data suggest that hepatic fat accumulation is reversible after stopping treatment with JUXTAPID, generally over 4 to 6 weeks, but whether histological sequelae remain is unknown, especially after long-term use. The long term consequences of hepatic steatosis associated with JUXTAPID treatment are unknown, including risk of progression to steatohepatitis and cirrhosis.

Elevations in Hepatic Transaminases

Elevations in alanine and/or aspartate transaminases (ALT and/or AST) associated with JUXTAPID treatment are generally dose-dependent, asymptomatic, and reversible (see ADVERSE REACTIONS). Liver enzyme changes occur most often during dose escalation, but may occur at any time during therapy. In clinical studies, there were no concomitant increases in serum bilirubin or alkaline phosphatase.

Hepatic transaminases, i.e., serum ALT, AST, should be measured before initiation of treatment with JUXTAPID, and prior to each dose escalation (see DOSAGE AND ADMINISTRATION). After the patient has been stabilized on an individualized dose, transaminases should be measured periodically, i.e., monthly during the first year of treatment and every three months after the first year.

Use with Hepatotoxic Agents

Caution should be exercised when JUXTAPID is co-administered with agents known to have a potential for hepatotoxicity, such as isotretinoin, amiodarone, acetaminophen in high doses, methotrexate, tetracyclines, and tamoxifen. The effect of concomitant administration of JUXTAPID with other hepatotoxic medications is unknown. More frequent monitoring of liver function tests may be warranted.

Alcohol Consumption

JUXTAPID should be used with caution in patients who consume alcohol because of its potential to induce or exacerbate hepatic injury, including steatosis. Limitation of alcohol use is warranted with JUXTAPID treatment, e.g., a limit of no more than one drink daily.

Risk of Severe Diarrhea and Dehydration

Use of lomitapide has been associated with severe diarrhea and dehydration. Caution should be exercised in vulnerable patients (e.g., geriatric patients, or patients taking diuretics) due to the subsequent risk of hypovolemia and hypotension.

Concomitant Use of CYP 3A4 Inhibitors

CYP 3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of strong or moderate CYP 3A4 inhibitors with JUXTAPID is contraindicated (see CONTRAINDICATIONS). If treatment with strong or moderate CYP 3A4 inhibitors is unavoidable, JUXTAPID should be stopped during the course of treatment.

Grapefruit juice must be omitted from the diet during treatment with JUXTAPID.

Weak CYP3A4 inhibitors are expected to increase the exposure of lomitapide when taken simultaneously. When administered with atorvastatin, the dose of JUXTAPID should either be taken 12 hours apart or be decreased by half. The dose of JUXTAPID should be administered 12 hours apart from any other weak CYP3A4 inhibitor (see DRUG INTERACTIONS, Drug-Drug Interactions, and DOSAGE AND ADMINISTRATION).

Concomitant Use with HMG-CoA Reductase Inhibitors

JUXTAPID increases plasma concentrations of statins. The risk of myopathy, including rhabdomyolysis, is dose related with use of statins. Lomitapide approximately doubles the exposure to simvastatin (see DRUG INTERACTIONS, Drug-Drug Interactions, Table 6). Accordingly, it is recommended to reduce the dose of simvastatin by 50% when initiating JUXTAPID. 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) (see CONTRAINDICATIONS).

The effect of lomitapide on the systemic exposure of other statins is less than that seen with simvastatin (see DRUG INTERACTIONS, Table 6), and is dependent both on the dose of statin and that of lomitapide administered. Dose adjustment of statin may be required (see DOSAGE AND ADMINISTRATION).

Use with Warfarin

Lomitapide increases the plasma concentrations of warfarin (see DRUG INTERACTIONS, Table 6). Patients taking warfarin should undergo more frequent monitoring of the INR, especially after any changes in JUXTAPID dosage (see DOSAGE AND ADMINISTRATION, Warfarin). As usual, the dose of warfarin should be adjusted as clinically indicated.

Use in Special Populations

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

Women of Child-Bearing Potential: Patients should be advised that JUXTAPID may cause birth defects based on animal studies. Before initiating treatment in women of child-bearing potential, the absence of pregnancy should be confirmed, appropriate advice on effective methods of contraception provided, and effective contraception initiated (see DOSAGE AND ADMINISTRATION). Oral contraceptives are weak CYP3A4 inhibitors; dosing with lomitapide should be separated by 12 hours (see DRUG INTERACTIONS). Patients taking estrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhea and/or vomiting. Additional contraceptive measures should be used until resolution of symptoms. Patients should be advised to immediately contact their health professional and stop taking JUXTAPID if they become pregnant while taking JUXTAPID.

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

Geriatrics: Clinical studies of JUXTAPID did not include sufficient numbers of patients with HoFH aged 65 years and over to determine whether they respond differently than younger patients. In general, dosing for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and concomitant drug therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Consistent with the mechanism of action of JUXTAPID (lomitapide), most treated patients exhibited gastrointestinal (GI) discomfort or other related GI adverse events (see DOSAGE AND ADMINISTRATION).

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

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

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

A total of 999 patients have been treated with JUXTAPID in 25 clinical studies, including 22 exposed for 1 year. Due to the rarity of the disease, a single pivotal registration trial was conducted in patients with HoFH. It was a single-arm, open-label study in 29 patients. Patients treated with JUXTAPID in this study included 16 males (55%) and 13 females (45%); mean age of the population was 30.7 years, and ranged from 18 to 55 years.

The common (≥10%) adverse events reported in patients with HoFH in the pivotal registration trial are presented in Table 1.

Table 1: Adverse Events Reported in ≥10% (≥3 subjects) of HoFH Patients (N=29)

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

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%).

Hepatic Transaminase Elevations

During the HoFH pivotal registration trial, 10 of 29 (34%) patients had at least one elevation in ALT and/or AST ≥3x ULN, see Table 2. 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 stopping JUXTAPID.

There was no consistent dose-response relationship that predicted onset of liver enzyme elevation. Among the 10 patients with elevations ≥3x ULN, the dose of JUXTAPID at the time of the initial maximum elevation in transaminase levels was 10 mg in 3 patients, 20 mg in 1 patient, 40 mg in 4 patients, and 60 mg in 2 patients. Decreasing or interrupting the dose of JUXTAPID resulted in predictable reductions in hepatic aminotransferase levels.

Table 2: Highest Liver Function Test Results Post First Dose in HoFH Patients

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

Among the 19 patients who enrolled in an extension study following the HoFH pivotal registration 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 interaction between JUXTAPID, and the strong CYP 3A4 inhibitor, clarithromycin.

Hepatic Steatosis

Hepatic fat was prospectively measured using magnetic resonance spectroscopy (MRS) in all eligible patients during the pivotal registration HoFH trial. Table 3 presents maximum changes in hepatic fat from baseline. Mean hepatic fat content was 1% at baseline. 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.

Table 3: Maximum Categorical Changes in % Hepatic Fat

MAXIMUM ABSOLUTE INCREASE IN % HEPATIC FAT	EFFICACY PHASE WEEKS 0-26 N (%)	SAFETY PHASE WEEKS 26-78 N (%)	ENTIRE TRIAL WEEKS 0-78 N (%)
Number of evaluable patients	22	22	23
≤5%	9 (41)	6 (27)	5 (22)
>5% to ≤10%	6 (27)	8 (36)	8 (35)
>10% to ≤15%	4 (18)	3 (14)	4 (17)
>15% to ≤20%	1 (5)	4 (18)	3 (13)
>20% to ≤25%	1 (5)	0	1 (4)
>25%	1 (5)	1 (5)	2 (9)

Non-HoFH Patient Population

Results from a pooled safety analysis of patients without HoFH but with elevated LDL-C and other cardiovascular risk factors demonstrated a similar pattern of adverse events (see Table 4) to that observed in HoFH patients (see Table 1). This pool comprises patients that were treated for multiple durations of treatment ranging from 2 to 12 weeks, and includes 462 patients with hypercholesterolemia, with or without additional risk factors for CV disease.

Table 4: Treatment-Emergent Adverse Events Reported in 5% or More of Patients in Studies that Evaluated Lomitapide Monotherapy in the Non-HoFH Study Pool (Safety Population)

PREFERRED TERM	LOMITAPIDE MONOTHERAPY (N=291) N (%)	PLACEBO (N=116) N (%)	ACTIVE CONTROL (N=55) N (%)
Diarrhea	163 (56.0)	13 (11.2)	4 (7.3)
Nausea	68 (23.4)	4 (3.4)	3 (5.5)
Flatulence	32 (11.0)	7 (6.0)	0
Headache	27 (9.3)	13 (11.2)	2 (3.6)
Abdominal Pain Upper	25 (8.6)	4 (3.4)	0
Abdominal Distension	24 (8.2)	4 (3.4)	3 (5.5)
Abdominal Pain	23 (7.9)	2 (1.7)	2 (3.6)
Alanine Aminotransferase Increased	22 (7.6)	1 (0.9)	1 (1.8)
Fatigue	21 (7.2)	3 (2.6)	0
Vomiting	20 (6.9)	3 (2.6)	0
Aspartate Aminotransferase Increased	19 (6.5)	1 (0.9)	1 (1.8)
Dyspepsia	15 (5.2)	3 (2.6)	4 (7.3)
Back Pain	11 (3.8)	6 (5.2)	2 (3.6)
Nasopharyngitis	5 (1.7)	6 (5.2)	4 (7.3)

Less Common Clinical Trial Adverse Drug Reactions

Less common adverse events reported following treatment with lomitapide include the following, without attribution of causality:

Gastrointestinal disorders: dry mouth, eructation, gastroesophageal reflux, abdominal or epigastric discomfort, hematemesis, lower gastrointestinal hemorrhage, reflux esophagitis

Hepatobiliary disorders: hepatomegaly

Cardiovascular: myocardial infarction (1 case), chest pain

Infections: gastroenteritis, influenza, nasopharyngitis, sinusitis

Blood and lymphatic system disorders: anemia

Metabolism and nutrition disorders: dehydration, increased or decreased appetite, decreased weight

Nervous system disorders: paresthesia, dizziness, somnolence, transient ischemic attack (1 case)

Eye disorders: eye swelling

Ear and labyrinth disorders: vertigo

Respiratory, thoracic and mediastinal disorders: pharyngeal lesion, cough

Skin and subcutaneous tissue disorders: hyperhidrosis, rash, pruritus

Musculoskeletal and connective tissue disorders: arthralgia, myalgia, pain in extremity, joint swelling, muscle twitching

Renal and urinary disorders: hematuria

General Disorders and administrative site conditions: asthenia, chills, early satiety, gait disturbance, malaise, pyrexia, anxiety, hypersensitivity

Laboratory Investigations: blood bilirubin increased, gamma-glutamyltransferase increased, neutrophil percentage increased, protein urine, prothrombin time (INR) prolonged, pulmonary function test abnormal, white blood cell count increased.

Abnormal Laboratory Findings

A thorough review of hematology, renal function, electrolytes, serum protein and creatine phosphokinase, did not reveal any effect of lomitapide on these parameters.

Post Marketing Experience:

The following adverse reaction has 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.

Skin reactions: Alopecia

DRUG INTERACTIONS

Overview

CYP 3A4 is the isozyme primarily responsible for the metabolism of JUXTAPID (lomitapide). Lomitapide does not induce CYP 1A2, 3A4, or 2B6. Lomitapide inhibits CYP 3A4. Lomitapide does not inhibit CYP 1A2, 2B6, 2C9, 2C19, 2D6, or 2E1.

The major metabolites of lomitapide, M1 and M3, do not induce CYP 1A2, 3A4, or 2B6. M1 and M3 do not inhibit CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4.

Lomitapide is not a P-gp substrate. Lomitapide inhibits P-gp (see DOSAGE AND ADMINISTRATION, Dosing Considerations) but does not inhibit breast cancer resistance protein (BCRP).

Drug-Drug Interactions

Effect of Other Drugs on Lomitapide

Table 5 summarizes the effect of coadministered ketoconazole, atorvastatin and ethinyl estradiol/norgestimate on lomitapide AUC and C_{max}.

Table 5: Effect of Coadministered Drugs on Lomitapide Systemic Exposure

COADMINISTERED DRUG	DOSING OF COADMINISTERED DRUG	DOSING OF LOMITAPIDE	RATIO OF LOMITAPIDE EXPOSURE WITH/WITHOUT COADMINISTERED DRUG NO EFFECT = 1			
			AUC		C_{max}	
Ketoconazole *	200 mg BID for 9 days	60 mg QD	↑ 27-fold		↑ 15-fold	
			Simultaneous dosing	Separated dosing†	Simultaneous dosing	Separated dosing†
Atorvastatin	80 mg QD	20 mg QD	↑2-fold	↑1.3	↑2-fold	↑1.3
Ethinyl Estradiol/norgestimate	0.035 mg EE/0.25 mg norgestimate QD	20 mg QD	↑1.3	↑1.2	↑1.4	↑1.3

*** Contraindicated with lomitapide** (see CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS, Concomitant Use of CYP 3A4 inhibitors)
† Dosing separated by 12 hours
BID = twice daily; QD = once daily
↑ = increase

CYP 3A4 Inhibitors

Concomitant CYP 3A4 inhibitor use increases lomitapide exposure. Lomitapide exposure increased 27-fold in the presence of ketoconazole, a strong CYP 3A4 inhibitor. Thus, concomitant use of strong CYP 3A4 inhibitors and lomitapide is contraindicated. The effect of moderate CYP 3A4 inhibitors on lomitapide exposure has not been studied. However, moderate CYP 3A4 inhibitors would be expected to increase lomitapide exposure several-fold based on experience with concomitant use of strong and weak CYP 3A4 inhibitors. Thus, concomitant use of moderate CYP 3A4 inhibitors and lomitapide is contraindicated (see CONTRAINDICATIONS).

When lomitapide was co-administered with weak CYP 3A4 inhibitors, e.g., atorvastatin, ethinyl estradiol/norgestimate, increases in lomitapide exposure were noted, see Table 5, above (see also DOSAGE AND ADMINISTRATION, Cytochrome P450 3A4 Inhibitors).

Effect of Lomitapide on Other Drugs

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

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

COADMINISTERED DRUG	DOSING OF COADMINISTERED DRUG	DOSING OF LOMITAPIDE	CHANGE OF COADMINISTERED DRUG EXPOSURE WITH / WITHOUT LOMITAPIDE)		
				AUC	C_{max}
Dosage adjustment necessary when coadministered with lomitapide					
Simvastatin[a]	40 mg single dose	60 mg QD × 7 days	Simvastatin Simvastatin acid	↑ 99% ↑ 71%	↑ 102% ↑ 57%
	20 mg single dose	10 mg QD x 7 days	Simvastatin Simvastatin acid	↑ 62% ↑ 39%	↑65% ↑ 35%
Warfarin[b]	10 mg single dose	60 mg QD x 12 days	R(+) warfarin S(-) warfarin INR	↑ 28% ↑ 30% ↑ 7%	↑ 14% ↑ 15% ↑ 22%
No dosing adjustments required for the following:					
Atorvastatin	20 mg single dose 20 mg single dose	60 mg QD × 7 days 10 mg QD × 7 days	Atorvastatin acid Atorvastatin acid	↑ 52% ↑ 11%	↑63% ↑19%
Rosuvastatin	20 mg single dose 20 mg single dose	60 mg QD × 7 days 10 mg QD × 7 days	Rosuvastatin Rosuvastatin	↑ 32% ↑ 2%	↑ 4% ↑ 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 ezetimibe	↑ 6%	↑ 3%
Extended-release niacin	1,000 mg single dose	10 mg QD × 7 days	Nicotinic acid Nicotinuric acid	↑ 10% ↓ 21%	↑ 11% ↓ 15%
Ethinyl estradiol	0.035 mg QD x 28 days	50 mg QD x 8 days	Ethinyl estradiol	↓ 8%	↓ 8%
Norgestimate	0.25 mg QD x 28 days	50 mg QD x 8 days	17-Deacetyl norgestimate	↑ 6%	↑ 2%

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

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

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

Drug-Food Interactions

Since grapefruit juice is a moderately strong inhibitor of CYP 3A4, patients taking JUXTAPID should avoid consumption of grapefruit juice (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Treatment with JUXTAPID (lomitapide) should be initiated and monitored by a physician experienced in the treatment of familial hypercholesterolemia. JUXTAPID should be used as an adjunct to a low-fat diet and other lipid-lowering drugs, in the treatment of HoFH (see INDICATIONS AND CLINICAL USE).

Appropriate control of the fat content in the diet is essential to reduce the occurrence and severity of gastrointestinal side effects associated with the use of JUXTAPID. Patients should follow a diet supplying less than 20% of energy from fat prior to initiating JUXTAPID treatment, and should continue this diet during treatment. Dietary counseling should be provided.

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 dietary supplements that contain 400 international units vitamin E and at least 200 mg linoleic acid, 210 mg alpha linoleic acid (ALA), 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA). These dietary supplements should not be taken within a two hour window of JUXTAPID administration. For example, it may be convenient for dietary supplements to be taken in the morning.

JUXTAPID should be taken without food (see Administration, below). JUXTAPID administration with food increases systemic exposure to lomitapide (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, *Absorption*). JUXTAPID administration with food may also increase the incidence of gastrointestinal adverse events, and so should be avoided.

Patients with end-stage renal disease receiving dialysis should not exceed 40 mg JUXTAPID daily. There are no data available to guide dosing in other patients with renal impairment.

Patients with mild hepatic impairment (Child-Pugh A) should not exceed 40 mg JUXTAPID daily (see ACTION AND CLINICAL PHARMACOLOGY, Hepatic Insufficiency). JUXTAPID is contraindicated in patients with moderate to severe hepatic impairment (see CONTRAINDICATIONS).

Women of Reproductive Potential: JUXTAPID is contraindicated during pregnancy (see CONTRAINDICATIONS). Before initiating treatment in women of reproductive potential, the absence of pregnancy should be confirmed, appropriate advice on effective methods of contraception provided, and effective contraception initiated, as appropriate. Oral contraceptives are weak CYP3A4 inhibitors; dosing with lomitapide should be separated by 12 hours (see DRUG INTERACTIONS). Patients taking estrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhea and/or vomiting. If the patient becomes pregnant while taking JUXTAPID, the patient should immediately stop taking JUXTAPID and contact their health professional.

Concomitant Use with HMG-CoA Reductase Inhibitors: JUXTAPID increases plasma concentrations of statins. Dose reduction of statins may be required, especially with simvastatin, to mitigate risk of statin-induced myopathy, including rhabdomyolysis (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Concomitant Use with HMG-CoA Reductase Inhibitors, and DRUG INTERACTIONS, Table 6).

Cytochrome P450 3A4 Inhibitors: JUXTAPID is contraindicated with concomitant use of strong and moderate CYP 3A4 inhibitors (see CONTRAINDICATIONS).

When concomitantly used with atorvastatin, a weak CYP3A4 inhibitor, JUXTAPID should either be taken separately, i.e., 12 hours apart, or the dose of JUXTAPID should be reduced by 50%.

When concomitantly used with any other weak CYP3A4 inhibitor, such as alprazolam, amiodarone, amlodipine, azithromycin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, lapatinib, nilotinib, oral contraceptives, pazopanib, peppermint oil, ranitidine, ranolazine, Seville oranges, ticagrelor, tolvaptan, and zileuton, separate the dose of the medications, i.e., JUXTAPID and the weak CYP 3A4 inhibitor, by 12 hours (see DRUG INTERACTIONS).

Consider limiting the maximum daily dose of JUXTAPID according to desired LDL-C response.

Exercise additional caution if administering more than one (1) weak CYP3A4 inhibitor with JUXTAPID.

Grapefruit Juice: Patients taking JUXTAPID should avoid consumption of grapefruit juice (see WARNINGS AND PRECAUTIONS, Concomitant Use of CYP 3A4 Inhibitors, and DRUG INTERACTIONS, Drug-Food Interactions).

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

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.

Warfarin: JUXTAPID increases the plasma concentrations of warfarin (see DRUG INTERACTIONS, Table 6). Increases in the dose of JUXTAPID may lead to supratherapeutic anticoagulation. Under circumstances when lomitapide dosage may be decreased, subtherapeutic anticoagulation may occur. Patients taking warfarin should undergo more frequent monitoring of the INR following initiation of lomitapide, or after dosage changes. It is suggested that INR be measured weekly, until a stable dose of JUXTAPID has been achieved for at least 2 weeks.

Recommended Dose and Dosage Adjustment

The dose of JUXTAPID should be escalated gradually to minimize the incidence and severity of gastrointestinal side effects. The recommended starting dose is 5 mg once daily. After 2 weeks, the dose may be increased, based on acceptable safety and tolerability, to 10 mg, and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and the maximum recommended dose of 60 mg as described in Table 7. Modify dosing for patients taking concomitant CYP 3A4 inhibitors, renal impairment, or baseline hepatic impairment.

Table 7: 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

Hepatic transaminases (ALT, AST), alkaline phosphatase, and total bilirubin should be measured before initiation of treatment with JUXTAPID. During the first year, measure liver-related tests, especially ALT and/or AST, prior to each increase in dose or monthly, whichever occurs first. (see WARNINGS AND PRECAUTIONS, Risk of Hepatotoxicity, *Elevations in Hepatic Transaminases*).

Table 8 summarizes recommendations for dosage adjustment and monitoring for patients who develop elevated transaminases during therapy with JUXTAPID, see Table 8, below.

Table 8: Dosage Adjustment and Monitoring in Patients with Elevated Transaminases

ALT OR AST	TREATMENT AND MONITORING RECOMMENDATIONS*
≥3x and <5x ULN	• Confirm elevation with a repeat measurement within one week. • If confirmed, reduce the dose and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR). • Repeat tests weekly and stop JUXTAPID 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, investigate to identify the probable cause. • If resuming JUXTAPID after transaminases resolve to <3x ULN, consider reducing the dose and monitor liver-related tests more frequently.
≥5x ULN	• Stop JUXTAPID, obtain additional liver-related tests (such as alkaline phosphatase, total bilirubin, and INR), and investigate to identify the probable cause. • If resuming JUXTAPID after transaminases resolve to <3x ULN, reduce the dose and monitor liver-related tests more frequently.

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

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

Consistent with its mechanism of action, increases in absolute hepatic fat content may be expected in patients treated with lomitapide (see WARNINGS AND PRECAUTIONS, Risk of Hepatotoxicity, *Hepatic Steatosis*, and ADVERSE REACTIONS, Table 3). The long term consequences of hepatic steatosis associated with JUXTAPID treatment are unknown, including risk of progression to steatohepatitis, fibrosis and cirrhosis. Accordingly, baseline assessment of hepatic fibrosis should be carried out using appropriate imaging technology, and subsequently repeated on an intermittent basis. Baseline and subsequent intermittent assessment using laboratory markers of hepatic inflammation, as well as of fibrosis, should also be instituted to identify the potential development of steatohepatitis, fibrosis and cirrhosis.

Missed Dose

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, the healthcare provider should be contacted before restarting treatment.

Administration

JUXTAPID should be taken once a day with a glass of water, without food, at least 2 hours after the evening meal, because administration with food may adversely impact gastrointestinal tolerability of JUXTAPID.

Patients should swallow JUXTAPID capsules whole. Capsules should not be opened, crushed dissolved, or chewed.

OVERDOSAGE

There is no specific treatment in the event of overdosage of JUXTAPID (lomitapide). 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.

The maximum dose administered to human subjects in clinical studies was 200 mg lomitapide, as a single dose, without adverse consequences.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

JUXTAPID (lomitapide) is a potent, selective inhibitor of microsomal triglyceride transfer protein (MTP), an intracellular lipid-transfer protein that is found in the lumen of the endoplasmic reticulum and is responsible for binding and shuttling individual lipid molecules between membranes. MTP plays a key role in the assembly of apo B containing lipoproteins in the liver and intestines. Inhibition of MTP impairs the synthesis of chylomicrons and VLDL. The inhibition of the synthesis of VLDL leads to reduced levels of plasma LDL-C. Lomitapide has a mechanism of action that differs from those of other classes of lipid lowering agents (e.g., statins, bile acid sequestrants, cholesterol absorption inhibitors). This distinct mechanism appears to be complementary to that of other lipid-lowering agents, as listed just above.

Pharmacokinetics

Absorption: Upon oral administration of a single 60-mg dose of lomitapide, its T_{max} is around 6 (4-8) hours in healthy volunteers. The absolute bioavailability of lomitapide is approximately 7%, limited primarily by an extensive first-pass effect. Lomitapide pharmacokinetics is approximately dose-proportional for oral single doses from 10-100 mg.

Lomitapide C_{max} and AUC were increased following a high-fat meal (77% and 58%, respectively), or a low-fat meal (70% and 28%, respectively).

Distribution: The mean lomitapide volume of distribution at steady-state is 985-1,292 L. 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*. CYP 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 itself 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.

Special Populations and Conditions

Gender: There was no clinically relevant effect of gender on the pharmacokinetics of JUXTAPID.

Race: No dose adjustment is required for Caucasian or Latino patients. There is insufficient information to determine if JUXTAPID requires dose adjustment in other races. However, since JUXTAPID is dosed in an escalating fashion according to individual patient response, no adjustment to the dosing regimen is recommended for JUXTAPID administration based on race.

Hepatic Insufficiency: 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).

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

QT Study:

At a concentration of 23 times the C_{max} of the maximum recommended dose of lomitapide, no clinically relevant prolongation of QT_c was observed.

STORAGE AND STABILITY

Store at 15°C to 30°C. Keep container tightly closed and protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms:

JUXTAPID Capsules 5 mg:
Each capsule contains 6 mg lomitapide mesylate equivalent to 5 mg free base. Orange/orange hard gelatin capsule printed with black ink "A733" and "5 mg."

JUXTAPID Capsules 10 mg:
Each capsule contains 11 mg lomitapide mesylate equivalent to 10 mg free base. Orange/white hard gelatin capsule printed with black ink "A733" and "10 mg."

JUXTAPID Capsules 20 mg:
Each capsule contains 23 mg lomitapide mesylate equivalent to 20 mg free base. White/white hard gelatin capsule printed with black ink "A733" and "20 mg."

Capsule Composition:

Each capsule contains either 6, 11 or 23 mg lomitapide mesylate, equivalent to 5 mg, 10 mg, and 20 mg free base respectively, as the active ingredient. Each capsule also contains the following non-medicinal ingredients: gelatin, lactose white monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, red iron oxide (5mg and 10 mg only), silicon dioxide, sodium starch glycolate, titanium dioxide.

Packaging:

All strengths (5 mg, 10 mg and 20 mg) are available in bottles of 28 capsules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: lomitapide mesylate

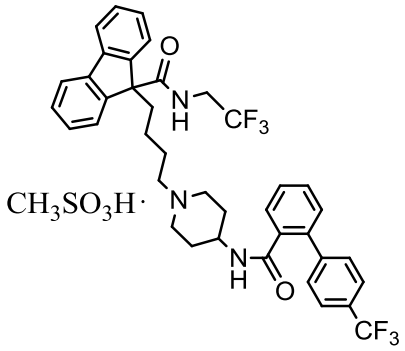
Chemical name: N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9*H*-fluorene-9-carboxamide, methanesulfonate salt

Molecular formula: $C_{39}H_{37}F_6N_3O_2 \bullet CH_4O_3S$

Molecular mass of lomitapide mesylate: 789.8 g/mol

Molecular mass of lomitapide (free base): 693.7 g/mol

Structural formula:



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

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

CLINICAL TRIALS

The effects of JUXTAPID (lomitapide) on LDL-C, TC, apo B, TG, and HDL-C, when added to a low-fat diet and other lipid-lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH) are presented in Table 9, below.

The safety and effectiveness of JUXTAPID as an adjunct to a low-fat diet and other lipid-lowering treatments at optimized doses, including LDL apheresis where available, were evaluated in a multinational, single-arm, open-label, pivotal registration trial involving 29 adults with HoFH. A diagnosis of HoFH was defined by the presence of at least one of the following clinical criteria: (1) documented functional mutation(s) in both LDL receptor alleles or alleles known to affect LDL receptor functionality, or (2) skin fibroblast LDL receptor activity <20% normal, or (3) untreated TC >500 mg/dL and TG <300 mg/dL and both parents with documented untreated TC >250 mg/dL.

Among the 29 patients enrolled, the mean age was 30.7 years (range, 18 to 55 years), 16 (55%) were men, and the majority (86%) were Caucasian. The mean body mass index (BMI) was 25.8 kg/m2, 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.

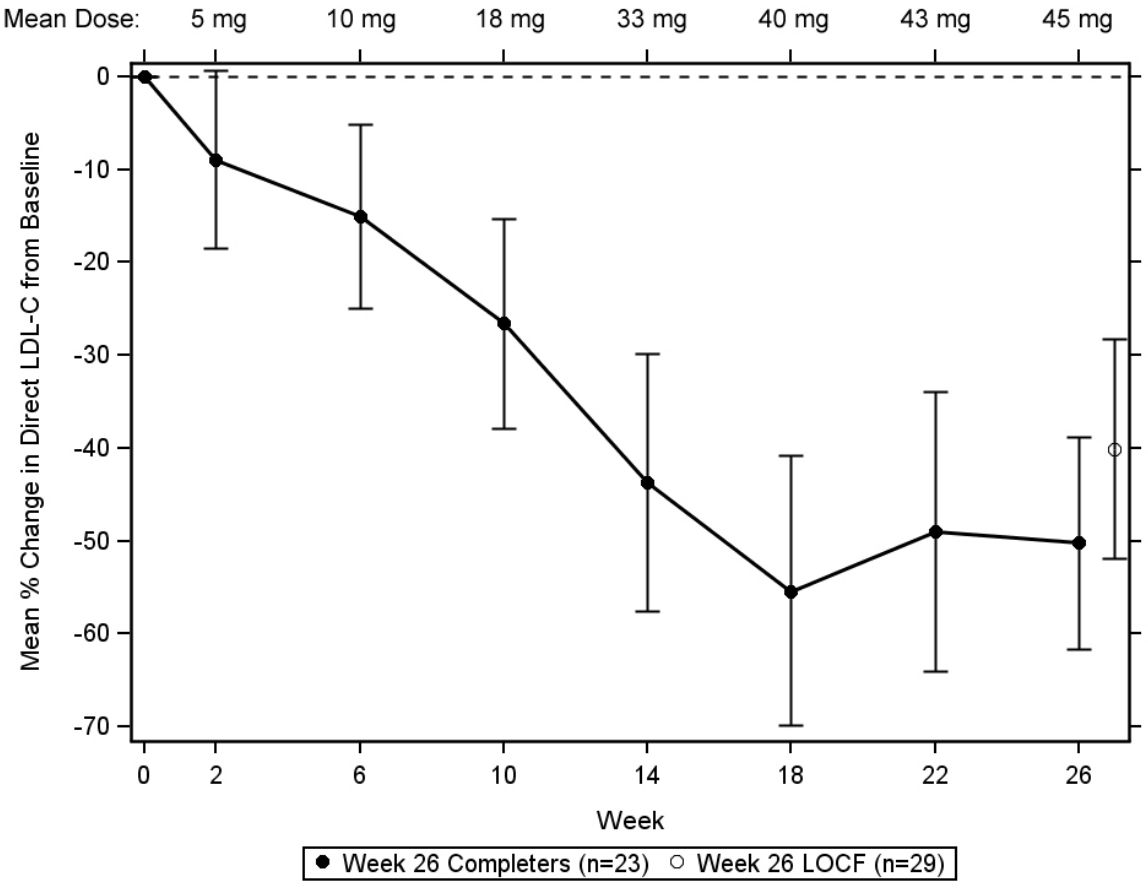
After a six-week run-in period to stabilize lipid-lowering treatments, including the establishment of an LDL apheresis schedule if applicable, JUXTAPID was initiated at 5 mg daily and titrated to daily doses of 10 mg, 20 mg, 40 mg, and 60 mg at weeks 2, 6, 10, and 14, respectively, based on tolerability 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. 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 Changes in LDL-C in the HoFH Pivotal Registration Study, from Baseline (Week 26 Completers)



Error bars represent 95% confidence intervals of the mean.

Changes in lipids and lipoproteins through Week 26 and Week 56 of JUXTAPID treatment are presented in Table 9.

Table 9: Absolute Values and Percent Changes from Baseline to Weeks 26 and 56 in Lipids and Lipoproteins in HoFH Patients

PARAMETER	UNITS	BASELINE	WEEK 26/LOCF (N=29)			WEEK 56 (N=23)		
		Mean (SD)	Mean (SD)	% Change[b]	p-value[c]	Mean (SD)	% Change[b]	p-value[c]
LDL-C, direct	mg/dL	336 (114)	190 (104)	-40	<0.001	199 (123)	-44	<0.001
	mmol/L	8.7 (3.0)	4.9 (2.7)			5.2 (3.2)		
TC	mg/dL	430 (135)	258 (118)	-36	<0.001	274 (144)	-39	<0.001
	mmol/L	11.1 (3.5)	6.7 (3.1)			7.1 (3.7)		
apo B	mg/dL	259 (80)	148 (74)	-39	<0.001	149 (83)	-45	<0.001
	mmol/L	6.7 (2.1)	3.8 (1.9)			3.9 (2.1)		
TG[a]	mg/dL	92	57	-45	0.009	61	-33	0.004
	mmol/L	1.0	0.6			0.7		
Non-HDL-C	mg/dL	386 (132)	217 (113)	-40	<0.001	229 (139)	-44	<0.001
	mmol/L	10.0 (3.4)	5.6 (2.9)			5.9 (3.6)		
VLDL-C	mg/dL	21 (10)	13 (9)	-29	0.012	16 (14)	-28	0.005
	mmol/L	0.5 (0.3)	0.3 (0.2)			0.4 (0.4)		
Lp(a)[a]	nmol/L	66	61	-13	0.094	56	-21	<0.001
HDL-C	mg/dL	44 (11)	41 (13)	-7	0.072	45 (15)	+1	0.920
	mmol/L	1.1 (0.3)	1.1 (0.3)			1.2 (0.4)		

[a] Median presented for TG and Lp(a). p-value is based on the mean percent change
[b] The % change values are calculated based on gravimetric units
[c] p--value on the mean percent change from baseline based on paired t-test

For the 23 of 29 HoFH patients who completed 78 weeks of lomitapide treatment, the mean LDL-C values were 210 mg/dL (5.4 mmol/L), a mean change of 38%. For these patients, the baseline mean LDL-C was 352 mg/dL (9.1 mmol/L).

At baseline, 93% of patients were on a statin; 76% were on ezetimibe; 10% were on niacin; 3% were on a bile acid sequestrant; and 62% were receiving apheresis. Fourteen of 23 (61%) patients had their baseline concomitant lipid-lowering treatment (LLT) reduced by Week 56, including planned and unplanned reductions/interruptions. Apheresis was discontinued in 3 of 13 patients who were on it at Week 26, while its frequency was reduced in 1 patient, while maintaining acceptable LDL-C levels through Week 56 in all four. Of the 23 patients who completed through Week 26, 19 (83%) had LDL-C reductions ≥25%, with 8 (35%) having LDL-C < 100 mg/dL (2.6 mmol/L), and 1 having LDL-C <70 mg/dL (1.8 mmol/L) at that time point.

The demographic characteristics of the HoFH population were similar in the Phase 2 (UP1001) and pivotal registration (Study UP1002/AEGR-733-005) studies (Table 10).

All 35 patients met the protocol-defined HoFH diagnostic criteria. Mean Baseline LDL-C for the 6 patients in the Phase 2 study was markedly elevated at 614.2 mg/dL (15.9 mmol/L) as these patients were required to be off all LLT within 4 weeks of study entry. In the pivotal registration study, where patients were required to be on a stable regimen of their LLT, mean Baseline LDL-C was also elevated at 336.0 mg/dL (8.7 mmol/L) despite their use of standard of care therapies.

Table 10: Demographics and Baseline Characteristics, HoFH Study Pool (Full Analysis Set)

CHARACTERISTIC	STUDY UP1001 (N=6)	STUDY UP1002/ 733-005 (N=29)
Age (years)		
Mean (SD)	25.0 (9.19)	30.7 (10.56)
Minimum, Maximum	17, 39	18, 55
Number (%) Male	3 (50.0)	16 (55.2)
Number (%) Caucasian	3 (50.0)	25 (86.2)
BMI (kg/m^2), n (%)		
<30	5 (83.3)	25 (86.2)
≥30	1 (16.7)	4 (13.8)
Baseline LDL-C (mg/dL)		
Mean (SD)	614.2 (105.85)[1]	336.0 (113.75)
Minimum, Maximum	480, 789	152, 565
Baseline LDL-C (mmol/L)		
Mean (SD)	15.9 (2.74)[1]	8.7 (2.94)
Minimum, Maximum	12, 20	4, 15

[1] Subjects were required to be off all LLTs within 4 weeks of study entry.

Overall, 27 (93%) of the 29 patients in the pivotal registration study were on optimized doses of HMG-CoA reductase inhibitors (statins) at study entry, primarily rosuvastatin (45%) and atorvastatin (31%); 17% of patients were receiving simvastatin. A total of 76% of patients were receiving ezetimibe, all coadministered with a statin; 10% were on niacin and 3% were on a bile acid sequestrant. Eighteen (62%) of the 29 patients were receiving apheresis at baseline in the pivotal registration study. As detailed in Table 10, all 6 patients in the Phase 2 study were required to be off all other LLT.

TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year dietary carcinogenicity study in mice, lomitapide was administered at doses of 0.3, 1.5, 7.5, 15, or 45 mg/kg/day. There were statistically significant increases in the incidences of liver adenomas and carcinomas in males at doses ≥1.5 mg/kg/day (≥2-times the MRHD at 60 mg based on AUC) and in females at ≥7.5 mg/kg/day (≥10-times the human exposure at 60 mg based on AUC). Incidences of small intestinal carcinomas in males and combined adenomas and carcinomas in females were significantly increased at doses ≥15 mg/kg/day (≥23-times the human exposure at 60 mg based on AUC).

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

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

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

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3. Cuchel M, Meagher EA, Theron H. dT, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolemia: a single-arm, open-label, phase 3 study. Lancet 2013 Jan 5; 381 (9860): 40-46

PART III: CONSUMER INFORMATION

JUXTAPID
lomitapide capsules

This leaflet is part III of a three-part "Product Monograph" published when JUXTAPID was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about JUXTAPID. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
JUXTAPID is a medicine for adults with very high cholesterol because of a condition that runs in families called homozygous familial hypercholesterolemia or HoFH. JUXTAPID works along with a low-fat diet and other lipid-lowering drugs, with or without LDL apheresis, to lower cholesterol.

What it does:
JUXTAPID works by blocking the action of microsomal triglyceride transfer protein (MTP). This protein is located within the liver and the gut cells, where it is involved in assembling fatty substances into larger particles that are then released into the blood stream. By blocking this protein, the medicine decreases the level of fats and cholesterol in the blood, thereby helping to control the disease process.
JUXTAPID lowers blood levels of LDL cholesterol ("bad cholesterol").

When it should not be used:
Do not take JUXTAPID if you:

- have liver problems or unexplained abnormal liver tests
- have stomach or bowel problems (such as inflammatory bowel disease) or cannot absorb food properly from your bowel
- are taking more than 20 mg simvastatin, unless you have been instructed by your doctor to take 40 mg simvastatin daily, and tolerated it well
- are pregnant, trying to get pregnant, or think you may be pregnant
- are breast-feeding, because it is not known if the medicine is passed into breast milk
- drink more than one alcoholic beverage a day
- drink grapefruit juice
- are allergic (hypersensitive) to lomitapide or any of the other ingredients of JUXTAPID capsules
- Have one of the following rare hereditary diseases:
    - Galactose intolerance
    - Lapp lactase deficiency
    - Glucose-galactose malabsorption

  because lactose is a non-medicinal ingredient in JUXTAPID.

What the medicinal ingredient is:
lomitapide mesylate

What the nonmedicinal ingredients are:
Gelatin, lactose white monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, red iron oxide (5mg and 10 mg capsules only), silicon dioxide, sodium starch glycolate, titanium dioxide.

What dosage forms it comes in:
Capsules; 5 mg, 10 mg, 20 mg

WARNINGS AND PRECAUTIONS

Possible Liver Disorder/Damage
JUXTAPID may cause liver damage and a fatty liver. The chance of liver damage is higher if you take statins, such as atorvastatin or simvastatin. Drinking alcohol may also raise your chance of liver damage. Your doctor will check your liver with blood tests before you start JUXTAPID, when your dose is increased, and regularly while you are taking JUXTAPID. These blood tests help your doctor adjust your dose. If your tests show some liver problems, your doctor may decide to stop JUXTAPID.

Pregnancy, the effect of JUXTAPID on an unborn child and the need for effective birth control
If you are a woman who can have children, your doctor must test you for pregnancy before prescribing JUXTAPID. Your pregnancy test must be negative for you to get JUXTAPID. JUXTAPID may harm an unborn child. Use effective birth control while you are taking JUXTAPID. Do not have unprotected sex.
Birth control pills may not work as well especially if you have diarrhea or vomiting. If you use birth control pills, use an additional (extra) form of birth control while you are on JUXTAPID.

If you become pregnant while taking JUXTAPID, stop taking JUXTAPID and contact your health professional immediately.

BEFORE you use JUXTAPID talk to your doctor or pharmacist if:

- you have **Gastrointestinal Disorders** including nausea, vomiting or belly pain, that gets worse, does not go away, or changes. These can occur if you do not eat a low fat diet while taking JUXTAPID. These side effects can also be symptoms of **Liver Disorder/Damage**
- you have or ever had liver problems, including liver problems while taking other medicines
- you have intestine or bowel problems
- you have problems digesting certain foods or cannot eat dairy products
- you drink alcohol (beer, wine, or liquor)
- you have serious kidney disease
- you have unexplained muscle pain, tenderness, or weakness

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

Do not take JUXTAPID if you are taking any of the following medications:

- For fungus infection: itraconazole, ketoconazole, fluconazole
- For bacterial infection: telithromycin, clarithromycin, erythromycin
- For viral or HIV infection: indinavir, nelfinavir, tipranavir/ritonavir, saquinavir
- For high blood pressure: diltiazem, verapamil
- For abnormal heart rhythms: dronedarone
- For depression: nefazodone

Drugs that may interact with JUXTAPID include:

- The blood thinner warfarin
- The statins, atorvastatin or simvastatin. JUXTAPID, taken with a statin, may increase the risk of muscle weakness
- Bile acid sequestrants (resins), such as colesevelam and cholestyramine
- Medicines for bacteria, fungus, or HIV infection
- Medicines for depression or high blood pressure
- Drugs known to be hard on the liver such as isotretinoin, amiodarone, high doses of acetaminophen , methotrexate, tetracyclines, tamoxifen, alchohol
- Birth control pills. They may not be effective
- The following drugs and herbal preparations may require the dose of JUXTAPID to be decreased: alprazolam, amlodipine, atorvastatin, azithromycin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, lapatinib, nilotinib, oral contraceptives, pazopanib, peppermint oil, ranitidine, ranolazine, ticagrelor, tolvaptan, zileuton
- The dose of the following drugs may need to be decreased if you take JUXTAPID: aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotonib, posaconazole, saxagliptin, simvastatin, sirolimus, sitagliptin, talinolol, tolvaptan, and topotecan

Foods that may interact with JUXTAPID include:

- Grapefruit juice.
- Seville oranges

Do not consume these while taking JUXTAPID.

PROPER USE OF THIS MEDICATION

JUXTAPID should only be prescribed by a physician experienced in the treatment of familial hypercholesterolemia.

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

JUXTAPID works along with other lipid-lowering drugs, with or without LDL apheresis and with a low-fat diet. The low-fat diet should be started before JUXTAPID use and continued throughout treatment. It will help reduce or control side effects related to **Gastrointestinal Disorders.** Continue these treatments as prescribed by your doctor.

Also, your doctor should prescribe Vitamin E and essential fatty acids for you to take each day while you take JUXTAPID. These should not be taken at the same time as JUXTAPID. Always take these supplements at least two hours before or after a JUXTAPID dose. It is recommended that dietary supplements be taken in the morning. Ask your doctor, nurse, or dietitian how to add them to your diet.

Usual Adult Dose of dietary supplements:

Daily Amount	
Vitamin E	400 IU
Omega-3: Eicosapentaenoic acid (EPA) Docosahexaenoic acid (DHA) Alpha linoleic acid (ALA)	 110 mg 80 mg 210 mg
Omega-6: Linoleic acid	200 mg

Instructions for how to take JUXTAPID

To minimize side effects, the dose is increased gradually.

How to Take JUXTAPID:

- **on an empty stomach**
- with water
- once a day at bedtime, at least two hours after your evening meal. Food can cause **Gastrointestinal Disorders** with JUXTAPID.
- swallow capsules whole (DO NOT open, crush, dissolve or chew).

Recommended Adult Starting Dose: 5 mg once a day.

Your doctor may increase the dose after two weeks and, then again after every 4 weeks.

Maximum Adult Recommended Dose: 60 mg a day.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If a dose of JUXTAPID is missed, take your normal dose at the usual time the next day. Do not double dose. If dosing is interrupted for more than a week, your doctor should be contacted before restarting treatment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

- Fatty liver

JUXTAPID can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	**Gastrointestinal Disorders:** Nausea, vomiting, diarrhea, flatulence, stomach cramping or pain, indigestion, decreased appetite, belching or burping	**X**		
	Myopathy/ Rhabdo-myolysis: Muscle pain or spasm that you cannot explain, muscle tenderness or weakness, dark brown urine		**x**	
Uncommon	**Liver Disorder/ Damage:** yellowing of the skin or eyes, fever, dark urine, or loss of appetite, abdominal pain, nausea, or vomiting that gets worse, does not go away or changes		**x**	
Uncommon	Severe diarrhea, associated with lightheadedness, decreased urine output, or tiredness			**x**
	Weight loss	**x**		
	Hair loss: hair falling out in large clumps, burning sensation of the scalp	**x**		

This is not a complete list of side effects. For any unexpected effects while taking JUXTAPID, contact your doctor or pharmacist.

HOW TO STORE IT

Keep this medicine out of the sight and reach of children. Store at 15°C to 30°C. Keep the bottle tightly closed in order to protect from moisture.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.aegerion.ca
or by contacting the sponsor, Aegerion Pharmaceuticals (Canada) Ltd., at:
439 University Avenue
Toronto, ON, Canada M5G 1Y8

This leaflet was prepared by Aegerion Pharmaceuticals (Canada) Ltd.
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