# ANNEX I

# SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Lojuxta 5 mg hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains lomitapide mesylate equivalent to 5 mg lomitapide.

Excipient with known effect
Each hard capsule contains 70.12 mg of lactose (as monohydrate) (see section 4.4).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Capsule, hard.

The capsule is an orange cap/orange body hard capsule of 19.4 mm, printed with black ink imprinted with “5 mg” on body and “A733” on cap.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Lojuxta is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH).

Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism) must be excluded.

### 4.2 Posology and method of administration

Treatment with Lojuxta should be initiated and monitored by a physician experienced in the treatment of lipid disorders.

Posology

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 to the maximum recommended dose of 60 mg (see section 4.8).

The dose should be escalated gradually to minimise the incidence and severity of gastrointestinal side effects and aminotransferase elevations.

Administration with food may increase exposure to Lojuxta. Lojuxta should be taken on an empty stomach, at least 2 hours after the evening meal because the fat content of a recent meal may adversely impact gastrointestinal tolerability.

The occurrence and severity of gastrointestinal adverse reactions associated with the use of Lojuxta decreases in the presence of a low fat diet. Patients should follow a diet supplying less than 20% of energy from fat prior to initiating Lojuxta treatment, and should continue this diet during treatment. Dietary counselling should be provided.

Patients should avoid consumption of grapefruit juice (see sections 4.4 and 4.5).

For patients on a stable maintenance dose of Lojuxta who receive atorvastatin either:

- Separate the dose of the medications by 12 hours

OR

- Decrease the dose of Lojuxta by half.

Patients on 5 mg should remain on 5 mg.
Careful titration may then be considered according to LDL-C response and safety/tolerability.
Upon discontinuation of atorvastatin the dose of Lojuxta should be up-titrated according to LDL-C response and safety/tolerability.

For patients on a stable maintenance dose of Lojuxta who receive any other weak CYP3A4 inhibitor, separate the dose of the medications (Lojuxta and the weak CYP3A4 inhibitor) by 12 hours.

Consider limiting the maximum dose of Lojuxta according to desired LDL-C response.
Exercise additional caution if administering more than 1 weak CYP3A4 inhibitor with Lojuxta.

Based on observations of decreased essential fatty acid and vitamin E levels in clinical trials, patients should take daily dietary supplements that provide 400 IU vitamin E and approximately 200 mg linoleic acid, 110 mg eicosapentaenoic acid (EPA), 210 mg alpha linolenic acid (ALA) and 80 mg docosahexaenoic acid (DHA) per day, throughout treatment with Lojuxta.

*Elderly population*

There is limited experience with Lojuxta in patients aged 65 years or older. Therefore, particular caution should be exercised in these patients.

Since the recommended dose regimen involves starting at the low end of the dosing range and escalating cautiously according to individual patient tolerability, no adjustment to the dosing regimen is recommended for the elderly.

*Hepatic impairment*

Lojuxta is contraindicated in patients with moderate or severe hepatic impairment including patients with unexplained persistent abnormal liver function tests (see section 5.2).

Patients with mild hepatic impairment (Child-Pugh A) should not exceed 40 mg daily.

*Renal impairment*

Patients with end-stage renal disease receiving dialysis should not exceed 40 mg daily (see section 5.2).

*Paediatric population*

The safety and efficacy of Lojuxta in children <18 years have not been established and the use of this medicinal product in children is therefore not recommended. No data are available.

Method of administration

Oral use.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests.
- Patients with a known significant or chronic bowel disease such as inflammatory bowel disease or malabsorption.
- Concomitant administration of >40 mg simvastatin (see section 4.5).
- Concomitant use of Lojuxta with strong or moderate cytochrome P450 (CYP) 3A4 inhibitors (e.g., antifungal azoles such as itraconazole, fluconazole,ketoconazole, voriconazole, posaconazole; macrolide antibiotics such as erythromycin or clarithromycin; ketolide antibiotics such as telithromycin; HIV protease inhibitors; the calcium channel blockers diltiazem and verapamil, and the anti-arrhythmic dronedarone [see section 4.5]).
- Pregnancy (see section 4.6).

## 4.4 Special warnings and precautions for use

Liver enzyme abnormalities and liver monitoring

Lomitapide can cause elevations in alanine aminotransferase [ALT] and aspartate aminotransferase [AST] and hepatic steatosis. The extent to which lomitapide-associated hepatic steatosis promotes the elevations in aminotransferase is unknown. Although cases of hepatic dysfunction (elevated aminotransferase with increase in bilirubin or International Normalized Ratio [INR]) or hepatic failure have not been reported, there is concern that lomitapide could induce steatohepatitis, which can progress to cirrhosis over several years. The clinical studies supporting the safety and efficacy of lomitapide in HoFH would have been unlikely to detect this adverse outcome given their size and duration.

Elevations in aminotransferases (ALT and/or AST) are associated with lomitapide (see section 5.1). There were no concomitant or subsequent clinically meaningful elevations in serum bilirubin, INR, or alkaline phosphatase. Liver enzyme changes occur most often during dose escalation, but may occur at any time during therapy.

Monitoring of liver function tests

Measure ALT, AST, alkaline phosphatase, total bilirubin, gamma-glutamyl transferase (gamma-GT) and serum albumin before initiation of treatment with Lojuxta. The medicinal product is contraindicated in patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests. If the baseline liver-related tests are abnormal, consider initiating the medicinal product after appropriate investigation by a hepatologist and the baseline abnormalities are explained or resolved.

During the first year, measure liver-related tests (ALT and AST, at a minimum) prior to each increase in dose or monthly, whichever occurs first. After the first year, do these tests at least every 3 months and before any increase in dose. Decrease the dose of Lojuxta if elevations of aminotransferase are observed and discontinue treatment for persistent or clinically significant elevations (see Table 1 for specific recommendations).

Dose modification based on elevated hepatic aminotransferases

Table 1 summarizes recommendations for dose adjustment and monitoring for patients who develop elevated aminotransferase during therapy with Lojuxta.

**Table 1: Dose Adjustment and Monitoring for Patients with Elevated Aminotransferases**

| ALT or AST | Treatment and monitoring recommendations* |
|---|---|
| ≥3x and <5x Upper Limit of Normal (ULN) | • Confirm elevation with a repeat measurement within one week.<br>• If confirmed, reduce the dose and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR).<br>• Repeat tests weekly and withhold dosing if there are signs of abnormal liver function (increase in bilirubin or INR), if aminotransferase levels rise above 5x ULN, or if aminotransferase levels do not fall below 3x ULN within approximately 4 weeks. Refer patients with persistent elevations in aminotransferase >3x ULN to a hepatologist for further investigation.<br>• If resuming Lojuxta after aminotransferase levels resolve to <3x ULN, consider reducing the dose and monitor liver-related tests more frequently. |
| ≥5x ULN | • Withhold dosing and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR). If aminotransferase levels do not fall below 3x ULN within approximately 4 weeks refer the patient to a hepatologist for further investigation.<br>• If resuming Lojuxta after aminotransferase levels 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 aminotransferase 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 Lojuxta and refer the patient to a hepatologist for further investigation.

Reintroduction of treatment may be considered if the benefits are considered to outweigh the risks associated with potential liver disease.

Hepatic steatosis and risk of progressive liver disease

Consistent with the mechanism of action of lomitapide, most treated patients exhibited increases in hepatic fat content. In an open-label Phase 3 study, 18 of 23 patients with HoFH developed hepatic steatosis (hepatic fat >5.56%) as measured by nuclear magnetic resonance spectroscopy (MRS) (see section 5.1). The median absolute increase in hepatic fat was 6% after both 26 weeks and 78 weeks of treatment, from 1% at baseline, measured by MRS. Hepatic steatosis is a risk factor for progressive liver disease including steatohepatitis and cirrhosis. The long term consequences of hepatic steatosis associated with Lojuxta treatment are unknown. Clinical data suggest that hepatic fat accumulation is reversible after stopping treatment with Lojuxta, but whether histological sequelae remain is unknown, especially after long-term use.

Monitoring for evidence of progressive liver disease.

Regular screening for steatohepatitis/fibrosis should be performed at baseline and on an annual basis using the following imaging and biomarker evaluations:

- Imaging for tissue elasticity, e.g. Fibroscan, acoustic radiation force impulse (ARFI), or magnetic resonance (MR) elastography

- Gamma-GT and serum albumin to detect possible liver injury

- At least one marker from each of the following categories:

    - High sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), CK-18 Fragment, NashTest (liver inflammation)
    - Enhanced Liver Fibrosis (ELF) panel, Fibrometer, AST/ALT ratio, Fib-4 score, Fibrotest (liver fibrosis)

The performance of these tests and their interpretation should involve collaboration between the treating physician and the hepatologist. Patients with results suggesting the presence of steatohepatitis or fibrosis should be considered for liver biopsy.

If a patient has biopsy-proven steatohepatitis or fibrosis, the benefit-risk should be reassessed and treatment stopped if necessary.

Dehydration

Post-marketing reports of dehydration and hospitalisation in patients treated with lomitapide have been reported. Patients treated with lomitapide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Concomitant use of CYP3A4 inhibitors

Lomitapide appears to be a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with Lojuxta is contraindicated (see section 4.3). In the lomitapide clinical trials, one patient with HoFH developed markedly elevated aminotransferase (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, Lojuxta should be stopped during the course of treatment.

Weak CYP3A4 inhibitors are expected to increase the exposure of lomitapide when taken simultaneously. When administered with atorvastatin, the dose of Lojuxta should either be taken 12 hours apart or be decreased by half (see section 4.2). The dose of Lojuxta should be administered 12 hours apart from any other weak CYP3A4 inhibitor.

Concomitant use of CYP3A4 inducers

Medicines that induce CYP3A4 would be expected to increase the rate and extent of metabolism of lomitapide. CYP3A4 inducers exert their effect in a time-dependent manner, and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2 weeks to decline.

Co-administration of a CYP3A4 inducer is expected to reduce the effect of Lojuxta. Any impact on efficacy is likely to be variable. When co-administering CYP3A4 inducers (i.e. aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, glucocorticoids, modafinil and phenytoin) with Lojuxta, the possibility of a drug-drug interaction affecting efficacy should be considered. The use of St. John's Wort should be avoided with Lojuxta.

It is recommended to increase the frequency of LDL-C assessment during such concomitant use and consider increasing the dose of Lojuxta to ensure maintenance of the desired level of efficacy if the CYP3A4 inducer is intended for chronic use. On withdrawal of a CYP3A4 inducer, the possibility of increased exposure should be considered and a reduction in the dose of Lojuxta may be necessary.

Concomitant use of HMG-CoA reductase inhibitors ('statins')

Lomitapide increases plasma concentrations of statins. Patients receiving Lojuxta as adjunctive therapy to a statin should be monitored for adverse events that are associated with the use of high doses of statins. Statins occasionally cause myopathy. In rare cases, myopathy may take the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and can lead to fatality. All patients receiving Lojuxta in addition to a statin should be advised of the potential increased risk of myopathy and told to report promptly any unexplained muscle pain, tenderness, or weakness. Doses of simvastatin >40 mg should not be used with Lojuxta (see section 4.3).

Grapefruit juice

Grapefruit juice must be omitted from the diet while patients are treated with Lojuxta.

Risk of supratherapeutic or subtherapeutic anticoagulation with coumarin based anticoagulants

Lomitapide increases the plasma concentrations of warfarin. Increases in the dose of Lojuxta may lead to supratherapeutic anticoagulation, and decreases in the dose may lead to subtherapeutic anticoagulation. Difficulty controlling INR contributed to early discontinuation from the Phase 3 trial for one of five patients taking concomitant warfarin. Patients taking warfarin should undergo regular monitoring of the INR, especially after any changes in Lojuxta dosage. The dose of warfarin should be adjusted as clinically indicated.

Use of alcohol

Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. In the Phase 3 trial, 3 of 4 patients with ALT elevations >5x ULN reported alcohol consumption beyond the limits recommended in the protocol. The use of alcohol during Lojuxta treatment is not recommended.

Hepatotoxic agents

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

Reduced absorption of fat-soluble vitamins and serum fatty acids

Given its mechanism of action in the small intestine, lomitapide may reduce the absorption of fat-soluble nutrients. In the Phase 3 trial, patients were provided daily dietary supplements of vitamin E, linoleic acid, ALA, EPA and 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 lomitapide treatment of up to 78 weeks. Patients treated with Lojuxta should take daily supplements that contain 400 international units vitamin E and approximately 200 mg linoleic acid, 210 mg ALA, 110 mg EPA, and 80 mg DHA.

Contraception measures in women of child-bearing potential

Before initiating treatment in women of child-bearing potential, appropriate advice on effective methods of contraception should be provided, and effective contraception initiated. Patients taking oestrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting (see section 4.5). Oestrogen-containing oral contraceptives are weak CYP3A4 inhibitors (see section 4.2).

Patients should be advised to immediately contact their physician and stop taking Lojuxta if they become pregnant (see section 4.6).

Lactose

Lojuxta contains lactose and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption.

## 4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on Lojuxta and other forms of interaction

**Table 2: Interactions between Lojuxta and other medicinal products and other forms of interaction**

| Medicinal products | Effects on lomitapide levels | Recommendation concerning co-administration with Lojuxta |
|---|---|---|
| Inhibitors of CYP3A4 | When lomitapide 60 mg was co-administered with ketoconazole 200 mg twice daily, a strong inhibitor of CYP3A4, lomitapide AUC increased approximately 27-fold and $C_{max}$ increased approximately 15-fold.<br><br>Interactions between moderate CYP3A4 inhibitors and lomitapide have not been studied.<br><br>Moderate CYP3A4 inhibitors are predicted to have a substantial impact on lomitapide's pharmacokinetics. Concomitant use of moderate CYP3A4 inhibitors are expected to increase lomitapide exposure by 4-10 fold based on the results of the study with the strong CYP3A4 inhibitor ketoconazole and on historical data for the model CYP3A4 probe midazolam.<br><br>Weak CYP3A4 inhibitors are expected to increase the exposure of lomitapide when taken simultaneously.<br><br>When lomitapide 20 mg was co-administered simultaneously with atorvastatin, a weak CYP3A4 inhibitor, lomitapide AUC and $C_{max}$ increased approximately 2-fold. When the dose of lomitapide was taken 12 hours apart from atorvastatin, | Use of strong or moderate inhibitors of CYP3A4 is contraindicated with Lojuxta. If treatment with antifungal azoles (e.g., itraconazole, ketoconazole, fluconazole, voriconazole, posaconazole); the antiarrhythmic dronedarone; macrolide antibiotics (e.g., erythromycin, clarithromycin); ketolide antibiotics (e.g., telithromycin); HIV protease inhibitors; the calcium channel blockers diltiazem and verapamil is unavoidable, therapy with Lojuxta should be suspended during the course of treatment (see sections 4.3 and 4.4).<br><br>Grapefruit juice is a moderate inhibitor of CYP3A4 and is expected to substantially increase exposure to lomitapide. Patients taking Lojuxta should avoid consumption of grapefruit juice.<br><br>When administered with atorvastatin, the dose of Lojuxta should either be taken 12 hours apart or be decreased by half (see section 4.2). The dose of Lojuxta should be taken 12 hours apart from any other concomitant weak CYP3A4 inhibitors. Examples of weak CYP3A4 inhibitors include: alprazolam, amiodarone, amlodipine, atorvastatin, azithromycin, bicalutamide, cilostazol, cimetidine, ciclosporin, clotrimazole, fluoxetine, fluvoxamine, fosaprepitant, ginkgo, goldenseal, isoniazid, ivacaftor, lacidipine, lapatinib, linagliptin, nilotinib, oestrogen-containing oral contraceptives, pazopanib, peppermint oil, propiverine, ranitidine, ranolazine, roxithromycin, Seville oranges, tacrolimus, ticagrelor and tolvaptan. This |

| Medicinal products | Effects on lomitapide levels | Recommendation concerning co-administration with Lojuxta |
|---|---|---|
| | no clinically meaningful increase in lomitapide exposure was observed.<br><br>When lomitapide 20 mg was co-administered simultaneously or 12 hours apart with ethinyl estradiol/norgestimate, a weak CYP3A4 inhibitor, no clinically meaningful increase in lomitapide exposure was observed. | list is not intended to be comprehensive and prescribers should check the prescribing information of drugs to be co-administered with Lojuxta for potential CYP3A4 mediated interactions.<br><br>The effect of administration of more than one weak CYP3A4 inhibitor has not been tested, but the effect on the exposure of lomitapide is expected to be greater than for co-administration of the individual inhibitors with lomitapide.<br><br>Exercise additional caution if administering more than 1 weak CYP3A4 inhibitor with Lojuxta. |
| Inducers of CYP3A4 | Medicines that induce CYP3A4 would be expected to increase the rate and extent of metabolism of lomitapide. Consequently, this would reduce the effect of lomitapide. Any impact on efficacy is likely to be variable. | When co-administering CYP3A4 inducers (i.e., aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, St John's Wort, glucocorticoids, modafinil and phenytoin) with Lojuxta, the possibility of a drug-drug interaction affecting efficacy should be considered. It is recommended to increase the frequency of LDL-C assessment during such concomitant use and consider increasing the dose of Lojuxta to ensure maintenance of the desired level of efficacy if the CYP3A4 inducer is intended for chronic use. |
| Bile acid sequestrants | Lomitapide has not been tested for interaction with bile acid sequestrants (resins such as colesevelam and cholestyramine). | Because bile acid sequestrants can interfere with the absorption of oral medicines, bile acid sequestrants should be taken at least 4 hours before or at least 4 hours after Lojuxta. |

Effects of lomitapide on other medicinal products

*HMG-CoA Reductase Inhibitors ("Statins"):* Lomitapide increases plasma concentrations of statins. When lomitapide 60 mg was administered to steady state prior to simvastatin 40 mg, simvastatin acid AUC and $C_{max}$ increased 68% and 57%, respectively. When lomitapide 60 mg was administered to steady state prior to atorvastatin 20 mg, atorvastatin acid AUC and $C_{max}$ increased 52% and 63%, respectively. When lomitapide 60 mg was administered to steady state prior to rosuvastatin 20 mg, rosuvastatin $T_{max}$ increased from 1 to 4 hours, AUC was increased 32%, and its $C_{max}$ was unchanged. The risk of myopathy with simvastatin is dose related. Use of Lojuxta is contraindicated in patients treated with high doses of simvastatin (>40 mg) (see sections 4.3 and 4.4).

*Coumarin anticoagulants:* When lomitapide 60 mg was administered to steady state and 6 days following warfarin 10 mg, INR increased 1.26-fold. AUCs for R(+)-warfarin and S(-)-warfarin increased 25% and 30%, respectively. $C_{max}$ for R(+)-warfarin and S(-)-warfarin increased 14% and 15%, respectively. In patients taking coumarins (such as warfarin) and Lojuxta concomitantly, INR

should be determined before starting Lojuxta and monitored regularly with dosage of coumarins adjusted as clinically indicated (see section 4.4).

*Fenofibrate, niacin and ezetimibe*: When lomitapide was administered to steady state prior to micronised fenofibrate 145 mg, extended release niacin 1000 mg, or ezetimibe 10 mg, no clinically significant effects on the exposure of any of these medicinal products were observed. No dose adjustments are required when co-administered with Lojuxta.

*Oral contraceptives:* When lomitapide 50 mg was administered to steady state along with an oestrogen-based oral contraceptive, no clinically meaningful or statistically significant impact on the pharmacokinetics of the components of the oral contraceptive (ethinyl estradiol and 17-deacetyl norgestimate, the metabolite of norgestimate) was observed. Lomitapide is not expected to directly influence the efficacy of oestrogen based oral contraceptives; however diarrhoea and/or vomiting may reduce hormone absorption. In cases of protracted or severe diarrhoea and/or vomiting lasting more than 2 days, additional contraceptive measures should be used for 7 days after resolution of symptoms.

*P-gp substrates:* Lomitapide inhibits P-gp *in vitro*, and may increase the absorption of P-gp substrates. Coadministration of Lojuxta 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 Lojuxta.

*In vitro assessment of drug interactions*: Lomitapide inhibits CYP3A4. Lomitapide does not induce CYPs 1A2, 3A4, or 2B6, and does not inhibit CYPs 1A2, 2B6, 2C9, 2C19, 2D6, or 2E1. Lomitapide is not a P-gp substrate but does inhibit P-gp. Lomitapide does not inhibit breast cancer resistance protein (BCRP).

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Lojuxta is contraindicated during pregnancy. There are no reliable data on its use in pregnant women. Animal studies have shown developmental toxicity (teratogenicity, embryotoxicity, see section 5.3). The potential risk for humans is unknown.

Use in women of child-bearing potential

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. Patients taking oestrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting. Additional contraceptive measures should be used until resolution of symptoms (see section 4.5).

Breast-feeding

It is not known whether lomitapide is excreted into human milk. Because of the potential for adverse effects based on findings in animal studies with lomitapide (see section 5.3), a decision should be made whether to discontinue breast-feeding or discontinue the medicinal product, taking into account the importance of the medicinal product to the mother.

Fertility

No adverse effects on fertility were observed in male and female rats administered lomitapide at systemic exposures (AUC) estimated to be 4 to 5 times higher than in humans at the maximum recommended human dose (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Lojuxta may have a minor influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile

The most serious adverse reactions during treatment were liver aminotransferase abnormalities (see section 4.4).

The most common adverse reactions were gastrointestinal effects. Gastrointestinal adverse reactions were reported by 27 (93%) of 29 patients in the Phase 3 clinical trial. Diarrhoea 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. Gastrointestinal adverse reactions occurred more frequently during the dose escalation phase of the study and decreased once patients established the maximum tolerated dose of lomitapide.

Gastrointestinal adverse reactions of severe intensity were reported by 6 (21%) of 29 patients in the Phase 3 clinical trial, with the most common being diarrhoea (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.

The most commonly reported adverse reactions of severe intensity were diarrhoea (4 subjects, 14%), vomiting (3 patients, 10%), and abdominal distension and ALT increased (2 subjects each, 7%).

Tabulated list of adverse reactions

Frequency of the adverse reactions is defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 3 lists all adverse reactions reported across the 35 patients treated in the Phase 2 Study UP1001 and in the Phase 3 Study UP1002/AEGR-733-005 or its extension study AEGR-733-012.

**Table 3: Frequency of Adverse Reactions in HoFH Patients**

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| Infections and infestations | Common | Gastroenteritis |
| Metabolism and nutrition disorders | Very common | Decreased appetite |
| | Not known | Dehydration |
| Nervous system disorders | Common | Dizziness<br>Headache<br>Migraine |
| Gastrointestinal disorders | Very common | Diarrhoea<br>Nausea<br>Vomiting<br>Abdominal discomfort<br>Dyspepsia<br>Abdominal pain<br>Abdominal pain upper<br>Flatulence<br>Abdominal distension<br>Constipation |
| | Common | Gastritis<br>Rectal tenesmus<br>Aerophagia<br>Defaecation urgency<br>Eructation<br>Frequent bowel movements<br>Gastric dilatation<br>Gastric disorder<br>Gastrooesophageal reflux disease<br>Haemorrhoidal haemorrhage<br>Regurgitation |
| Hepatobiliary disorders | Common | Hepatic steatosis<br>Hepatotoxicity<br>Hepatomegaly |
| Skin and subcutaneous tissue disorders | Common | Ecchymosis<br>Papule<br>Rash erythematous<br>Xanthoma |
| | Not known | Alopecia |
| Musculoskeletal and connective tissue disorders | Not known | Myalgia |
| General disorders and administration site conditions | Common | Fatigue |
| Investigations | Very common | Alanine aminotransferase increased<br>Aspartate aminotransferase increased<br>Weight decreased |
| | Common | International normalised ratio increased<br>Blood alkaline phosphatase increased<br>Blood potassium decreased<br>Carotene decreased<br>International normalised ratio abnormal<br>Liver function test abnormal<br>Prothrombin time prolonged<br>Transaminases increased<br>Vitamin E decreased<br>Vitamin K decreased |

Table 4 lists all adverse reactions for subjects who received lomitapide monotherapy (N=291) treated in Phase 2 studies in subjects with elevated LDL-C (N=462).

**Table 4: Frequency of Adverse Reactions in Elevated LDL-C Patients**

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| Infections and infestations | Uncommon | Gastroenteritis<br>Gastrointestinal infection<br>Influenza<br>Nasopharyngitis<br>Sinusitis |
| Blood and lymphatic system disorders | Uncommon | Anaemia |
| Metabolism and nutrition disorders | Common | Decreased appetite |
| | Uncommon | Dehydration<br>Increased appetite |
| Nervous system disorders | Uncommon | Paraesthesia<br>Somnolence |
| Eye disorders | Uncommon | Eye swelling |
| Ear and labyrinth disorders | Uncommon | Vertigo |
| Respiratory, thoracic and mediastinal disorders | Uncommon | Pharyngeal lesion<br>Upper-airway cough syndrome |
| Gastrointestinal disorders | Very common | Diarrhoea<br>Nausea<br>Flatulence |
| | Common | Abdominal pain upper<br>Abdominal distension<br>Abdominal pain<br>Vomiting<br>Abdominal discomfort<br>Dyspepsia<br>Eructation<br>Abdominal pain lower<br>Frequent bowel movements |
| | Uncommon | Dry mouth<br>Faeces hard<br>Gastrooeosophageal reflux disease<br>Abdominal tenderness<br>Epigastric discomfort<br>Gastric dilatation<br>Haematemesis<br>Lower gastrointestinal haemorrhage<br>Reflux oesophagitis |
| Hepatobiliary disorders | Uncommon | Hepatomegaly |
| Skin and subcutaneous tissue disorders | Uncommon | Blister<br>Dry skin<br>Hyperhidrosis |
| Musculoskeletal and connective tissue disorders | Common | Muscle spasms |
| | Uncommon | Arthralgia<br>Myalgia<br>Pain in extremity<br>Joint swelling<br>Muscle twitching |
| Renal and urinary disorders | Uncommon | Haematuria |

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| General disorders and administrative site conditions | Common | Fatigue<br>Asthenia |
| | Uncommon | Chest pain<br>Chills<br>Early satiety<br>Gait disturbance<br>Malaise<br>Pyrexia |
| Investigations | Common | Alanine aminotransferase increased<br>Aspartate aminotransferase increased<br>Hepatic enzyme increased<br>Liver function test abnormal<br>Neutrophil count decreased<br>White blood cell count decreased |
| | Uncommon | Weight decreased<br>Blood bilirubin increased<br>Gamma-glutamyltransferase increased<br>Neutrophil percentage increased<br>Protein urine<br>Prothrombin time prolonged<br>Pulmonary function test abnormal<br>White blood cell count increased |

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

There is no specific treatment in the event of overdose. In rodents, single oral doses of lomitapide ≥600 times higher than the maximum recommended human dose (1 mg/kg) were well tolerated. The maximum dose administered to human subjects in clinical studies was 200 mg as a single dose; there were no adverse reactions.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other lipid modifying agents, plain. ATC code: C10AX12

Mechanism of action

Lomitapide is a selective inhibitor of microsomal 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 reduces lipoprotein secretion and circulating concentrations of lipoprotein-borne lipids including cholesterol and triglycerides.

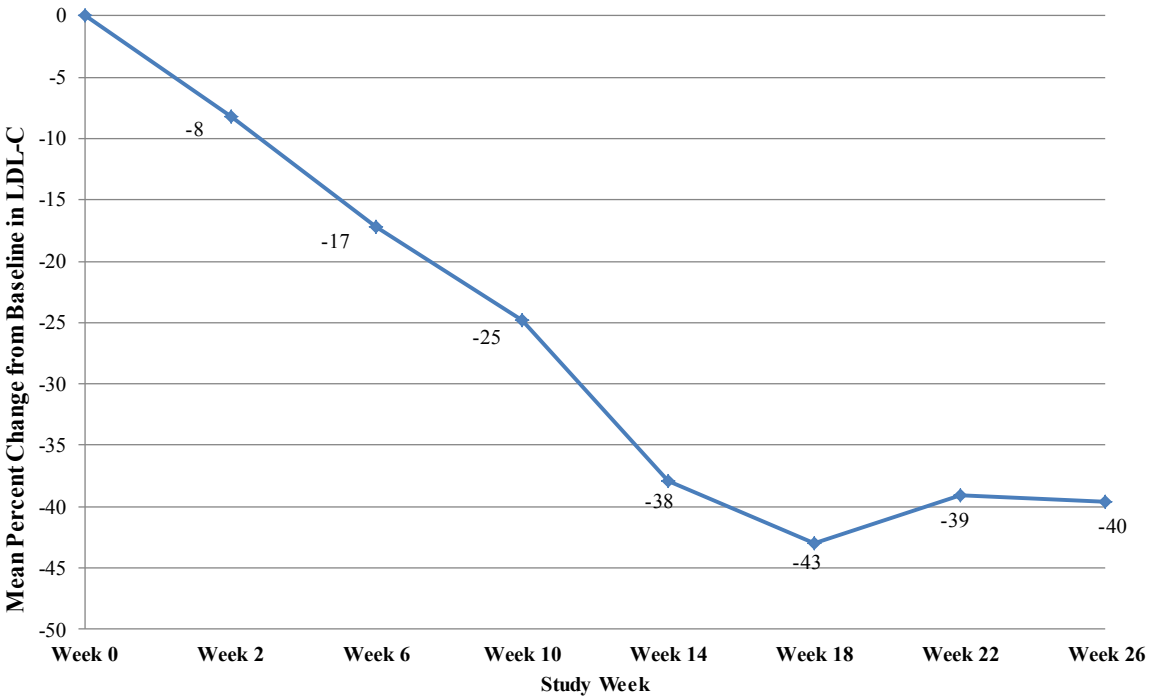
Clinical efficacy and safety

A single arm, open-label study (UP1002/AEGR-733-005) evaluated the efficacy and safety of lomitapide when co-administered with a low-fat diet and other lipid-lowering therapies in adult

patients with HoFH. Patients were instructed to maintain a low-fat diet (<20% calories from fat) and their lipid-lowering therapies at study entry, including apheresis if applicable, from 6 weeks prior to baseline through at least Week 26. The dose of lomitapide was escalated from 5 mg to an individually determined maximum tolerated dose up to 60 mg. After Week 26, patients remained on lomitapide to determine the effects of longer-term treatment and were allowed to change background lipid-lowering therapies. The study provided for a total of 78 weeks of treatment.

Twenty-nine patients were enrolled, of whom 23 completed through Week 78. Sixteen males (55%) and 13 females (45%) were included with a mean age of 30.7 years, ranging from 18 to 55 years. The mean dose of lomitapide was 45 mg at Week 26 and 40 mg at Week 78. At Week 26, the mean percent change in LDL-C from baseline of LDL-C was -40% ($p<0.001$) in the Intent to Treat (ITT) population. Mean percent change from baseline through Week 26 using last observation carried forward (LOCF) to each assessment is shown in Figure 1.

**Figure 1: Mean percent changes from baseline in LDL-C in the major effectiveness study UP1002/AEGR-733-005 through Week 26 (the Primary Endpoint) using LOCF to each assessment (N=29)**




Changes in lipids and lipoproteins through Week 26 and Week 78 of lomitapide treatment are presented in Table 5.

**Table 5: Absolute values and percent changes from baseline to Weeks 26 and 78 in lipids and lipoproteins (major effectiveness study UP1002/AEGR-733-005)**

| Parameter (units) | Baseline | Week 26/LOCF (N=29) | | | Week 78 (N=23) | | |
|---|---|---|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | % Change | p-value[b] | Mean (SD) | % Change | p-value[b] |
| LDL-C, direct (mg/dL) | 336 (114) | 190 (104) | -40 | <0.001 | 210 (132) | -38 | <0.001 |
| Total Cholesterol (TC) (mg/dL) | 430 (135) | 258 (118) | -36 | <0.001 | 281 (149) | -35 | <0.001 |
| Apolipoprotein B (apo B) (mg/dL) | 259 (80) | 148 (74) | -39 | <0.001 | 151 (89) | -43 | <0.001 |
| Triglycerides (TG) (mg/dL)[a] | 92 | 57 | -45 | 0.009 | 59 | -42 | 0.012 |
| Non high-density lipoprotein cholesterol (Non-HDL-C) (mg/dL) | 386 (132) | 217 (113) | -40 | <0.001 | 239 (146) | -39 | <0.001 |
| Very-low-density lipoprotein cholesterol (VLDL-C) (mg/dL) | 21 (10) | 13 (9) | -29 | 0.012 | 16 (15) | -31 | 0.013 |
| Lipoprotein (a) (Lp(a)) (nmol/L)[a] | 66 | 61 | -13 | 0.094 | 72 | -4 | <0.842 |
| High-density lipoprotein cholesterol (HDL-C) (mg/dL) | 44 (11) | 41 (13) | -7 | 0.072 | 43 (12) | -4.6 | 0.246 |

[a] Median presented for TG and Lp(a). p-value is based on the mean percent change
[b] p-value on the mean percent change from baseline based on paired t-test

At both Week 26 and Week 78, there were significant reductions in LDL-C, TC, apo B, TG, non-HDL-C, VLDL-C and changes in HDL-C trended lower at Week 26 and returned to baseline levels by Week 78.

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

At baseline, 93% were on a statin, 76% were on ezetimibe, 10% on niacin, 3% on a bile acid sequestrant and 62% were receiving apheresis. Fifteen of 23 (65%) patients had their lipid-lowering treatment reduced by Week 78, including planned and unplanned reductions/interruptions. Apheresis was discontinued in 3 out of 13 patients who were on it at Week 26, and frequency was reduced in 3 patients while maintaining low LDL-C levels through Week 78. The clinical benefit of reductions in background lipid-lowering therapy, including apheresis, is not certain.

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 and 1 having LDL-C <70 mg/dL at that time point.

In this study, 10 patients experienced elevations in AST and/or ALT >3 x ULN (see Table 6).

**Table 6: Highest liver function test results post first dose (major effectiveness study UP1002/AEGR-733-005)**

| **Parameter/Abnormality** | **N (%)** |
|---|---|
| ALT | |
| Number of Patients with Assessments | 29 |
| >3 to ≤5 x ULN | 6 (20.7) |
| >5 to ≤10 x ULN | 3 (10.3) |
| >10 to ≤20 x ULN | 1 (3.4) |
| >20 x ULN | 0 |
| AST | |
| Number of Patients with Assessments | 29 |
| >3 to ≤5 x ULN | 5 (17.2) |
| >5 to ≤10 x ULN | 1 (3.4) |
| >10 to ≤20 x ULN | 0 |
| >20 x ULN | 0 |

Elevations in ALT and/or AST >5 x ULN were managed with a dose reduction or temporary suspension of lomitapide dosing, and all patients were able to continue with study drug treatment. No clinically meaningful elevations in total bilirubin or alkaline phosphatase were observed. Hepatic fat was prospectively measured using MRS in all eligible patients during the clinical trial (Table 7). Data from individuals who had repeat measurements after stopping lomitapide show that hepatic fat accumulation is reversible, but whether histological sequelae remain is unknown.

**Table 7: Maximum categorical changes in % hepatic fat (major effectiveness study UP1002/AEGR-733-005)**

| **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) |

The European Medicines Agency has deferred the obligation to submit the results of studies with Lojuxta in one or more subsets of the paediatric population in HoFH (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption

The absolute oral bioavailability of lomitapide is 7%. Absorption is not limited by penetration of the drug across the intestinal barrier but is predominantly influenced by an extensive first pass effect. Peak plasma concentrations of lomitapide were reached 4-8 hours following oral dosing. Lomitapide pharmacokinetics is approximately dose-proportional for oral single doses in the therapeutic range. Doses higher than 60 mg suggest a trend toward nonlinearity and are not recommended.

Upon multiple dosing $C_{max}$ and AUC increased in approximate proportion to lomitapide dose. $C_{max}$ and AUC were increased following either a high-fat meal (77% and 58%, respectively) or low fat meal (70% and 28%, respectively). Accumulation of lomitapide in plasma was consistent with that predicted after a single dose following once daily oral dosing above 25 mg for up to 4 weeks. Inter-individual variability in lomitapide AUC was approximately 50%.

At steady state the accumulation of lomitapide was 2.7 at 25 mg and 3.9 at 50 mg.

Distribution

Following intravenous administration, the volume of distribution of lomitapide was high (mean=1200 litres) despite a high degree (>99.8%) of binding to plasma protein. In animal studies lomitapide was highly concentrated (200-fold) in the liver.

Biotransformation

Lomitapide is extensively metabolised, predominantly by CYP3A4. CYP isoforms 2E1, 1A2, 2B6, 2C8, and 2C19 are involved to a lesser extent and isoforms 2D6 and 2C9 are not involved in the metabolism of lomitapide.

Elimination

Following administration of a radiolabeled oral solution dose to healthy subjects, 93% of the administered dose was recovered in urine and faeces. Approximately 33% of the radioactivity was excreted in urine as metabolites. The remainder was excreted in faeces, primarily as oxidised metabolites. The elimination half-life of lomitapide was approximately 29 hours.

Special populations

Data in the pivotal clinical trial were analyzed with respect to the impact of potential covariates on lomitapide exposure. Of the parameters examined (race, body mass index (BMI), gender, weight, age), only BMI could be classified as a potential covariate.

*Age and gender*

There was no clinically relevant effect of age (18-64 years) or gender on the pharmacokinetics of lomitapide.

*Race*

No dose adjustment is required for Caucasian or Latino patients. There is insufficient information to determine if Lojuxta requires dose adjustment in other races. However, since the medicinal product is dosed in an escalating fashion according to individual patient safety and tolerability, no adjustment to the dosing regimen is recommended based on race.

*Renal insufficiency*

In the renal impairment population, lomitapide was only studied in patients with end-stage renal disease (ESRD). A pharmacokinetic study in patients with ESRD undergoing hemodialysis demonstrated a 36% increase in mean lomitapide plasma concentration compared to matched healthy controls. The terminal half-life of lomitapide was not affected.

*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. Lojuxta has not been studied in patients with severe hepatic impairment (Child-Pugh score 10-15).

*Paediatric population*

Lojuxta has not been investigated in children less than 18 years of age.

*Elderly population*

Lojuxta has not been investigated in patients aged 65 years or older.

**5.3 Preclinical safety data**

In repeat-dose oral toxicology studies in rodents and dogs, the principal drug-related findings were lipid accumulation in the small intestine and/or liver associated with decreases in serum cholesterol and/or triglyceride levels. These changes are secondary to the mechanism of action of lomitapide. Other liver-related changes in repeat-dose toxicity studies in rats and dogs included increased serum aminotransferases, subacute inflammation (rats only), and single-cell necrosis. In a 1 year repeat-dose study in dogs there were no microscopic changes in the liver although serum AST was minimally increased in females.

Pulmonary histiocytosis was observed in rodents. Decreased red blood cell parameters as well as poikilocytosis and/or anisocytosis were observed in dogs. Testicular toxicity was observed in dogs at 205 times the human exposure (AUC) at 60 mg in a 6-month study. No adverse effects on the testes were observed in a 1-year study in dogs at 64 times the human exposure at 60 mg.

In a dietary carcinogenicity study in mice, lomitapide was administered up to 104 weeks at doses ranging from 0.3 to 45 mg/kg/day. There were statistically significant increases in the incidences of liver adenoma and carcinoma at doses ≥1.5 mg/kg/day in males (≥ 2 times the human exposure at 60 mg daily based on AUC) and ≥7.5 mg/kg/day in females (≥ 9 times the human exposure at 60 mg based on AUC). Incidences of small intestinal carcinoma and/or combined adenoma and carcinoma (rare tumours in mice) were significantly increased at doses ≥15 mg/kg/day in males (≥ 26 times the human exposure at 60 mg based on AUC) and at 15 mg/kg/day in females (22 times the human exposure at 60 mg based on AUC).

In an oral carcinogenicity study in rats, lomitapide was administered up to 99 weeks at doses up to 7.5 mg/kg/day in males and 2.0 mg/kg/day in females. Focal hepatic fibrosis was observed in males and females and hepatic cystic degeneration was observed in males only. In high-dose males, an increased incidence of pancreatic acinar cell adenoma was observed at an exposure 6 times that in humans at 60 mg based on AUC.

Lomitapide was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* studies.

Lomitapide had no effect on reproductive function in female rats at doses up to 1 mg/kg or in male rats at doses up to 5 mg/kg. Systemic exposures to lomitapide at these doses were estimated to be 4 times (females) and 5 times (males) higher than the human exposure at 60 mg based on AUC.

Lomitapide was teratogenic in rats in the absence of maternal toxicity at an exposure (AUC) estimated to be twice that in humans at 60 mg. There was no evidence of embryofoetal toxicity in rabbits at 3 times the maximum recommended human dose (MRHD) of 60 mg based on body surface area. Embryofoetal toxicity was observed in rabbits in the absence of maternal toxicity at ≥6.5 times the MRHD. In ferrets, lomitapide was both maternally toxic and teratogenic at <1 times the MRHD.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule content
Pregelatinised starch (maize)
Sodium starch glycolate
Microcrystalline cellulose
Lactose monohydrate
Silica, colloidal anhydrous
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)

Printing ink
Shellac
Black iron oxide (E172)
Propylene glycol

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years.

### 6.4 Special precautions for storage

Store below 30°C.
Keep the bottle tightly closed in order to protect from moisture.

### 6.5 Nature and contents of container

High density polyethylene (HDPE) bottle fitted with a polyester/aluminium foil/cardboard induction seal and polypropylene screw cap.

Package sizes are:
28 capsules

### 6.6 Special precautions for disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Aegerion Pharmaceuticals Ltd
Lakeside House
1 Furzeground Way
Stockley Park East
Uxbridge UB11 1BD
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/851/001

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 July 2013

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Lojuxta 10 mg hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains lomitapide mesylate equivalent to 10 mg lomitapide.

Excipient with known effect
Each hard capsule contains 140.23 mg of lactose (as monohydrate) (see section 4.4).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Capsule, hard.

The capsule is an orange cap/white body hard capsule of 19.4 mm, printed with black ink imprinted with “10 mg” on body and “A733” on cap.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Lojuxta is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH).

Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism) must be excluded.

### 4.2 Posology and method of administration

Treatment with Lojuxta should be initiated and monitored by a physician experienced in the treatment of lipid disorders.

Posology

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 to the maximum recommended dose of 60 mg (see section 4.8).

The dose should be escalated gradually to minimise the incidence and severity of gastrointestinal side effects and aminotransferase elevations.

Administration with food may increase exposure to Lojuxta. Lojuxta should be taken on an empty stomach, at least 2 hours after the evening meal because the fat content of a recent meal may adversely impact gastrointestinal tolerability.

The occurrence and severity of gastrointestinal adverse reactions associated with the use of Lojuxta decreases in the presence of a low fat diet. Patients should follow a diet supplying less than 20% of energy from fat prior to initiating Lojuxta treatment, and should continue this diet during treatment. Dietary counselling should be provided.

Patients should avoid consumption of grapefruit juice (see sections 4.4 and 4.5).

For patients on a stable maintenance dose of Lojuxta who receive atorvastatin either:

- Separate the dose of the medications by 12 hours

OR

- Decrease the dose of Lojuxta by half.

Patients on 5 mg should remain on 5 mg.
Careful titration may then be considered according to LDL-C response and safety/tolerability.
Upon discontinuation of atorvastatin the dose of Lojuxta should be up-titrated according to LDL-C response and safety/tolerability.

For patients on a stable maintenance dose of Lojuxta who receive any other weak CYP3A4 inhibitor, separate the dose of the medications (Lojuxta and the weak CYP3A4 inhibitor) by 12 hours.

Consider limiting the maximum dose of Lojuxta according to desired LDL-C response.
Exercise additional caution if administering more than 1 weak CYP3A4 inhibitor with Lojuxta.

Based on observations of decreased essential fatty acid and vitamin E levels in clinical trials, patients should take daily dietary supplements that provide 400 IU vitamin E and approximately 200 mg linoleic acid, 110 mg eicosapentaenoic acid (EPA), 210 mg alpha linolenic acid (ALA) and 80 mg docosahexaenoic acid (DHA) per day, throughout treatment with Lojuxta.

*Elderly population*

There is limited experience with Lojuxta in patients aged 65 years or older. Therefore, particular caution should be exercised in these patients.

Since the recommended dose regimen involves starting at the low end of the dosing range and escalating cautiously according to individual patient tolerability, no adjustment to the dosing regimen is recommended for the elderly.

*Hepatic impairment*

Lojuxta is contraindicated in patients with moderate or severe hepatic impairment including patients with unexplained persistent abnormal liver function tests (see section 5.2).

Patients with mild hepatic impairment (Child-Pugh A) should not exceed 40 mg daily.

*Renal impairment*

Patients with end-stage renal disease receiving dialysis should not exceed 40 mg daily (see section 5.2).

*Paediatric population*

The safety and efficacy of Lojuxta in children < 18 years have not been established and the use of this medicinal product in children is therefore not recommended. No data are available.

Method of administration

Oral use.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests.
- Patients with a known significant or chronic bowel disease such as inflammatory bowel disease or malabsorption.
- Concomitant administration of >40 mg simvastatin (see section 4.5).
- Concomitant use of Lojuxta with strong or moderate cytochrome P450 (CYP) 3A4 inhibitors (e.g., antifungal azoles such as itraconazole, fluconazole,ketoconazole, voriconazole, posaconazole; macrolide antibiotics such as erythromycin or clarithromycin; ketolide antibiotics such as telithromycin; HIV protease inhibitors; the calcium channel blockers diltiazem and verapamil, and the anti-arrhythmic dronedarone [see section 4.5]).
- Pregnancy (see section 4.6).

## 4.4 Special warnings and precautions for use

Liver enzyme abnormalities and liver monitoring

Lomitapide can cause elevations in alanine aminotransferase [ALT] and aspartate aminotransferase [AST] and hepatic steatosis. The extent to which lomitapide-associated hepatic steatosis promotes the elevations in aminotransferase is unknown. Although cases of hepatic dysfunction (elevated aminotransferase with increase in bilirubin or International Normalized Ratio [INR]) or hepatic failure have not been reported, there is concern that lomitapide could induce steatohepatitis, which can progress to cirrhosis over several years. The clinical studies supporting the safety and efficacy of lomitapide in HoFH would have been unlikely to detect this adverse outcome given their size and duration.

Elevations in aminotransferases (ALT and/or AST) are associated with lomitapide (see section 5.1). There were no concomitant or subsequent clinically meaningful elevations in serum bilirubin, INR, or alkaline phosphatase. Liver enzyme changes occur most often during dose escalation, but may occur at any time during therapy.

Monitoring of liver function tests

Measure ALT, AST, alkaline phosphatase, total bilirubin, gamma-glutamyl transferase (gamma-GT) and serum albumin before initiation of treatment with Lojuxta. The medicinal product is contraindicated in patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests. If the baseline liver-related tests are abnormal, consider initiating the medicinal product after appropriate investigation by a hepatologist and the baseline abnormalities are explained or resolved.

During the first year, measure liver-related tests (ALT and AST, at a minimum) prior to each increase in dose or monthly, whichever occurs first. After the first year, do these tests at least every 3 months and before any increase in dose. Decrease the dose of Lojuxta if elevations of aminotransferase are observed and discontinue treatment for persistent or clinically significant elevations (see Table 1 for specific recommendations).

Dose modification based on elevated hepatic aminotransferases

Table 1 summarizes recommendations for dose adjustment and monitoring for patients who develop elevated aminotransferase during therapy with Lojuxta.

**Table 1: Dose Adjustment and Monitoring for Patients with Elevated Aminotransferases**

| ALT or AST | Treatment and monitoring recommendations* |
|---|---|
| ≥3x and <5x Upper Limit of Normal (ULN) | • Confirm elevation with a repeat measurement within one week.<br>• If confirmed, reduce the dose and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR).<br>• Repeat tests weekly and withhold dosing if there are signs of abnormal liver function (increase in bilirubin or INR), if aminotransferase levels rise above 5x ULN, or if aminotransferase levels do not fall below 3x ULN within approximately 4 weeks. Refer patients with persistent elevations in aminotransferase >3x ULN to a hepatologist for further investigation.<br>• If resuming Lojuxta after aminotransferase levels resolve to <3x ULN, consider reducing the dose and monitor liver-related tests more frequently. |
| ≥5x ULN | • Withhold dosing and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR). If aminotransferase levels do not fall below 3x ULN within approximately 4 weeks refer the patient to a hepatologist for further investigation.<br>• If resuming Lojuxta after aminotransferase levels 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 aminotransferase 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 Lojuxta and refer the patient to a hepatologist for further investigation.

Reintroduction of treatment may be considered if the benefits are considered to outweigh the risks associated with potential liver disease.

Hepatic steatosis and risk of progressive liver disease

Consistent with the mechanism of action of lomitapide, most treated patients exhibited increases in hepatic fat content. In an open-label Phase 3 study, 18 of 23 patients with HoFH developed hepatic steatosis (hepatic fat >5.56%) as measured by nuclear magnetic resonance spectroscopy (MRS) (see section 5.1). The median absolute increase in hepatic fat was 6% after both 26 weeks and 78 weeks of treatment, from 1% at baseline, measured by MRS. Hepatic steatosis is a risk factor for progressive liver disease including steatohepatitis and cirrhosis. The long term consequences of hepatic steatosis associated with Lojuxta treatment are unknown. Clinical data suggest that hepatic fat accumulation is reversible after stopping treatment with Lojuxta, but whether histological sequelae remain is unknown, especially after long-term use.

Monitoring for evidence of progressive liver disease.

Regular screening for steatohepatitis/fibrosis should be performed at baseline and on an annual basis using the following imaging and biomarker evaluations:

- Imaging for tissue elasticity, e.g. Fibroscan, acoustic radiation force impulse (ARFI), or magnetic resonance (MR) elastography

- Gamma-GT and serum albumin to detect possible liver injury

- At least one marker from each of the following categories:

    - High sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), CK-18 Fragment, NashTest (liver inflammation)
    - Enhanced Liver Fibrosis (ELF) panel, Fibrometer, AST/ALT ratio, Fib-4 score, Fibrotest (liver fibrosis)

The performance of these tests and their interpretation should involve collaboration between the treating physician and the hepatologist. Patients with results suggesting the presence of steatohepatitis or fibrosis should be considered for liver biopsy.

If a patient has biopsy-proven steatohepatitis or fibrosis, the benefit-risk should be reassessed and treatment stopped if necessary.

Dehydration

Post-marketing reports of dehydration and hospitalisation in patients treated with lomitapide have been reported. Patients treated with lomitapide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Concomitant use of CYP3A4 inhibitors

Lomitapide appears to be a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with Lojuxta is contraindicated (see section 4.3). In the lomitapide clinical trials, one patient with HoFH developed markedly elevated aminotransferase (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, Lojuxta should be stopped during the course of treatment.

Weak CYP3A4 inhibitors are expected to increase the exposure of lomitapide when taken simultaneously. When administered with atorvastatin, the dose of Lojuxta should either be taken 12 hours apart or be decreased by half (see section 4.2). The dose of Lojuxta should be administered 12 hours apart from any other weak CYP3A4 inhibitor.

Concomitant use of CYP3A4 inducers

Medicines that induce CYP3A4 would be expected to increase the rate and extent of metabolism of lomitapide. CYP3A4 inducers exert their effect in a time-dependent manner, and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2 weeks to decline.

Co-administration of a CYP3A4 inducer is expected to reduce the effect of Lojuxta. Any impact on efficacy is likely to be variable. When co-administering CYP3A4 inducers (i.e. aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, glucocorticoids, modafinil and phenytoin) with Lojuxta, the possibility of a drug-drug interaction affecting efficacy should be considered. The use of St. John’s Wort should be avoided with Lojuxta.

It is recommended to increase the frequency of LDL-C assessment during such concomitant use and consider increasing the dose of Lojuxta to ensure maintenance of the desired level of efficacy if the CYP3A4 inducer is intended for chronic use. On withdrawal of a CYP3A4 inducer, the possibility of increased exposure should be considered and a reduction in the dose of Lojuxta may be necessary.

Concomitant use of HMG-CoA reductase inhibitors ('statins')

Lomitapide increases plasma concentrations of statins. Patients receiving Lojuxta as adjunctive therapy to a statin should be monitored for adverse events that are associated with the use of high doses of statins. Statins occasionally cause myopathy. In rare cases, myopathy may take the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and can lead to fatality. All patients receiving Lojuxta in addition to a statin should be advised of the potential increased risk of myopathy and told to report promptly any unexplained muscle pain, tenderness, or weakness. Doses of simvastatin >40 mg should not be used with Lojuxta (see section 4.3).

Grapefruit juice

Grapefruit juice must be omitted from the diet while patients are treated with Lojuxta.

Risk of supratherapeutic or subtherapeutic anticoagulation with coumarin based anticoagulants

Lomitapide increases the plasma concentrations of warfarin. Increases in the dose of Lojuxta may lead to supratherapeutic anticoagulation, and decreases in the dose may lead to subtherapeutic anticoagulation. Difficulty controlling INR contributed to early discontinuation from the Phase 3 trial for one of five patients taking concomitant warfarin. Patients taking warfarin should undergo regular monitoring of the INR, especially after any changes in Lojuxta dosage. The dose of warfarin should be adjusted as clinically indicated.

Use of alcohol

Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. In the Phase 3 trial, 3 of 4 patients with ALT elevations >5x ULN reported alcohol consumption beyond the limits recommended in the protocol. The use of alcohol during Lojuxta treatment is not recommended.

Hepatotoxic agents

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

Reduced absorption of fat-soluble vitamins and serum fatty acids

Given its mechanism of action in the small intestine, lomitapide may reduce the absorption of fat-soluble nutrients. In the Phase 3 trial, patients were provided daily dietary supplements of vitamin E, linoleic acid, ALA, EPA and 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 lomitapide treatment of up to 78 weeks. Patients treated with Lojuxta should take daily supplements that contain 400 international units vitamin E and approximately 200 mg linoleic acid, 210 mg ALA, 110 mg EPA, and 80 mg DHA.

Contraception measures in women of child-bearing potential

Before initiating treatment in women of child-bearing potential, appropriate advice on effective methods of contraception should be provided, and effective contraception initiated. Patients taking oestrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting (see section 4.5). Oestrogen-containing oral contraceptives are weak CYP3A4 inhibitors (see section 4.2).

Patients should be advised to immediately contact their physician and stop taking Lojuxta if they become pregnant (see section 4.6).

Lactose

Lojuxta contains lactose and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption.

## 4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on Lojuxta and other forms of interaction

**Table 2: Interactions between Lojuxta and other medicinal products and other forms of interaction**

| Medicinal products | Effects on lomitapide levels | Recommendation concerning co-administration with Lojuxta |
|---|---|---|
| Inhibitors of CYP3A4 | When lomitapide 60 mg was co-administered with ketoconazole 200 mg twice daily, a strong inhibitor of CYP3A4, lomitapide AUC increased approximately 27-fold and $C_{max}$ increased approximately 15-fold.<br><br>Interactions between moderate CYP3A4 inhibitors and lomitapide have not been studied.<br><br>Moderate CYP3A4 inhibitors are predicted to have a substantial impact on lomitapide's pharmacokinetics. Concomitant use of moderate CYP3A4 inhibitors are expected to increase lomitapide exposure by 4-10 fold based on the results of the study with the strong CYP3A4 inhibitor ketoconazole and on historical data for the model CYP3A4 probe midazolam.<br><br>Weak CYP3A4 inhibitors are expected to increase the exposure of lomitapide when taken simultaneously.<br><br>When lomitapide 20 mg was co-administered simultaneously with atorvastatin, a weak CYP3A4 inhibitor, lomitapide AUC and $C_{max}$ increased approximately 2-fold. When the dose of lomitapide was taken 12 hours apart from atorvastatin, | Use of strong or moderate inhibitors of CYP3A4 is contraindicated with Lojuxta. If treatment with antifungal azoles (e.g., itraconazole, ketoconazole, fluconazole, voriconazole, posaconazole); the antiarrhythmic dronedarone; macrolide antibiotics (e.g., erythromycin, clarithromycin); ketolide antibiotics (e.g., telithromycin); HIV protease inhibitors; the calcium channel blockers diltiazem and verapamil is unavoidable, therapy with Lojuxta should be suspended during the course of treatment (see sections 4.3 and 4.4).<br><br>Grapefruit juice is a moderate inhibitor of CYP3A4 and is expected to substantially increase exposure to lomitapide. Patients taking Lojuxta should avoid consumption of grapefruit juice.<br><br>When administered with atorvastatin the dose of Lojuxta should either be taken 12 hours apart or be decreased by half (see section 4.2). The dose of Lojuxta should be taken 12 hours apart from any other concomitant weak CYP3A4 inhibitors. Examples of weak CYP3A4 inhibitors include: alprazolam, amiodarone, amlodipine, atorvastatin, azithromycin, bicalutamide, cilostazol, cimetidine, ciclosporin, clotrimazole, fluoxetine, fluvoxamine, fosaprepitant, ginkgo, goldenseal, isoniazid, ivacaftor, lacidipine, lapatinib, linagliptin, nilotinib, oestrogen-containing oral contraceptives, pazopanib, peppermint oil, propiverine, ranitidine, ranolazine, roxithromycin, Seville oranges, tacrolimus, ticagrelor and tolvaptan. This |

| Medicinal products | Effects on lomitapide levels | Recommendation concerning co-administration with Lojuxta |
|---|---|---|
| | no clinically meaningful increase in lomitapide exposure was observed.<br><br>When lomitapide 20 mg was co-administered simultaneously or 12 hours apart with ethinyl estradiol/norgestimate, a weak CYP3A4 inhibitor, no clinically meaningful increase in lomitapide exposure was observed. | list is not intended to be comprehensive and prescribers should check the prescribing information of drugs to be co-administered with Lojuxta for potential CYP3A4 mediated interactions.<br><br>The effect of administration of more than one weak CYP3A4 inhibitor has not been tested, but the effect on the exposure of lomitapide is expected to be greater than for co-administration of the individual inhibitors with lomitapide.<br><br>Exercise additional caution if administering more than 1 weak CYP3A4 inhibitor with Lojuxta. |
| Inducers of CYP3A4 | Medicines that induce CYP3A4 would be expected to increase the rate and extent of metabolism of lomitapide. Consequently, this would reduce the effect of lomitapide. Any impact on efficacy is likely to be variable. | When co-administering CYP3A4 inducers (i.e., aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, St John's Wort, glucocorticoids, modafinil and phenytoin) with Lojuxta, the possibility of a drug-drug interaction affecting efficacy should be considered. It is recommended to increase the frequency of LDL-C assessment during such concomitant use and consider increasing the dose of Lojuxta to ensure maintenance of the desired level of efficacy if the CYP3A4 inducer is intended for chronic use. |
| Bile acid sequestrants | Lomitapide has not been tested for interaction with bile acid sequestrants (resins such as colesevelam and cholestyramine). | Because bile acid sequestrants can interfere with the absorption of oral medicines, bile acid sequestrants should be taken at least 4 hours before or at least 4 hours after Lojuxta. |

Effects of lomitapide on other medicinal products

*HMG-CoA Reductase Inhibitors ("Statins"):* Lomitapide increases plasma concentrations of statins. When lomitapide 60 mg was administered to steady state prior to simvastatin 40 mg, simvastatin acid AUC and $C_{max}$ increased 68% and 57%, respectively. When lomitapide 60 mg was administered to steady state prior to atorvastatin 20 mg, atorvastatin acid AUC and $C_{max}$ increased 52% and 63%, respectively. When lomitapide 60 mg was administered to steady state prior to rosuvastatin 20 mg, rosuvastatin $T_{max}$ increased from 1 to 4 hours, AUC was increased 32%, and its $C_{max}$ was unchanged. The risk of myopathy with simvastatin is dose related. Use of Lojuxta is contraindicated in patients treated with high doses of simvastatin (>40 mg) (see sections 4.3 and 4.4).

*Coumarin anticoagulants:* When lomitapide 60 mg was administered to steady state and 6 days following warfarin 10 mg, INR increased 1.26-fold. AUCs for R(+)-warfarin and S(-)-warfarin increased 25% and 30%, respectively. $C_{max}$ for R(+)-warfarin and S(-)-warfarin increased 14% and 15%, respectively. In patients taking coumarins (such as warfarin) and Lojuxta concomitantly, INR

should be determined before starting Lojuxta and monitored regularly with dosage of coumarins adjusted as clinically indicated (see section 4.4).

*Fenofibrate, niacin and ezetimibe*: When lomitapide was administered to steady state prior to micronised fenofibrate 145 mg, extended release niacin 1000 mg, or ezetimibe 10 mg, no clinically significant effects on the exposure of any of these medicinal products were observed. No dose adjustments are required when co-administered with Lojuxta.

*Oral contraceptives:* When lomitapide 50 mg was administered to steady state along with an oestrogen-based oral contraceptive, no clinically meaningful or statistically significant impact on the pharmacokinetics of the components of the oral contraceptive (ethinyl estradiol and 17-deacetyl norgestimate, the metabolite of norgestimate) was observed. Lomitapide is not expected to directly influence the efficacy of oestrogen based oral contraceptives; however diarrhoea and/or vomiting may reduce hormone absorption. In cases of protracted or severe diarrhoea and/or vomiting lasting more than 2 days, additional contraceptive measures should be used for 7 days after resolution of symptoms.

*P-gp substrates:* Lomitapide inhibits P-gp *in vitro*, and may increase the absorption of P-gp substrates. Coadministration of Lojuxta 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 Lojuxta.

*In vitro assessment of drug interactions*: Lomitapide inhibits CYP3A4. Lomitapide does not induce CYPs 1A2, 3A4, or 2B6, and does not inhibit CYPs 1A2, 2B6, 2C9, 2C19, 2D6, or 2E1. Lomitapide is not a P-gp substrate but does inhibit P-gp. Lomitapide does not inhibit breast cancer resistance protein (BCRP).

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Lojuxta is contraindicated during pregnancy. There are no reliable data on its use in pregnant women. Animal studies have shown developmental toxicity (teratogenicity, embryotoxicity, see section 5.3). The potential risk for humans is unknown.

Use in women of child-bearing potential

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. Patients taking oestrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting. Additional contraceptive measures should be used until resolution of symptoms (see section 4.5).

Breast-feeding

It is not known whether lomitapide is excreted into human milk. Because of the potential for adverse effects based on findings in animal studies with lomitapide (see section 5.3), a decision should be made whether to discontinue breast-feeding or discontinue the medicinal product, taking into account the importance of the medicinal product to the mother.

Fertility

No adverse effects on fertility were observed in male and female rats administered lomitapide at systemic exposures (AUC) estimated to be 4 to 5 times higher than in humans at the maximum recommended human dose (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Lojuxta may have a minor influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile

The most serious adverse reactions during treatment were liver aminotransferase abnormalities (see section 4.4).

The most common adverse reactions were gastrointestinal effects. Gastrointestinal adverse reactions were reported by 27 (93%) of 29 patients in the Phase 3 clinical trial. Diarrhoea 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. Gastrointestinal adverse reactions occurred more frequently during the dose escalation phase of the study and decreased once patients established the maximum tolerated dose of lomitapide.

Gastrointestinal adverse reactions of severe intensity were reported by 6 (21%) of 29 patients in the Phase 3 clinical trial, with the most common being diarrhoea (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.

The most commonly reported adverse reactions of severe intensity were diarrhoea (4 subjects, 14%), vomiting (3 patients, 10%), and abdominal distension and ALT increased (2 subjects each, 7%).

Tabulated list of adverse reactions

Frequency of the adverse reactions is defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 3 lists all adverse reactions reported across the 35 patients treated in the Phase 2 Study UP1001 and in the Phase 3 Study UP1002/AEGR-733-005 or its extension study AEGR-733-012.

**Table 3: Frequency of Adverse Reactions in HoFH Patients**

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| Infections and infestations | Common | Gastroenteritis |
| Metabolism and nutrition disorders | Very common | Decreased appetite |
| | Not known | Dehydration |
| Nervous system disorders | Common | Dizziness<br>Headache<br>Migraine |
| Gastrointestinal disorders | Very common | Diarrhoea<br>Nausea<br>Vomiting<br>Abdominal discomfort<br>Dyspepsia<br>Abdominal pain<br>Abdominal pain upper<br>Flatulence<br>Abdominal distension<br>Constipation |
| | Common | Gastritis<br>Rectal tenesmus<br>Aerophagia<br>Defaecation urgency<br>Eructation<br>Frequent bowel movements<br>Gastric dilatation<br>Gastric disorder<br>Gastrooesophageal reflux disease<br>Haemorrhoidal haemorrhage<br>Regurgitation |
| Hepatobiliary disorders | Common | Hepatic steatosis<br>Hepatotoxicity<br>Hepatomegaly |
| Skin and subcutaneous tissue disorders | Common | Ecchymosis<br>Papule<br>Rash erythematous<br>Xanthoma |
| | Not known | Alopecia |
| Musculoskeletal and connective tissue disorders | Not known | Myalgia |
| General disorders and administration site conditions | Common | Fatigue |
| Investigations | Very common | Alanine aminotransferase increased<br>Aspartate aminotransferase increased<br>Weight decreased |
| | Common | International normalised ratio increased<br>Blood alkaline phosphatase increased<br>Blood potassium decreased<br>Carotene decreased<br>International normalised ratio abnormal<br>Liver function test abnormal<br>Prothrombin time prolonged<br>Transaminases increased<br>Vitamin E decreased<br>Vitamin K decreased |

Table 4 lists all adverse reactions for subjects who received lomitapide monotherapy (N=291) treated in Phase 2 studies in subjects with elevated LDL-C (N=462).

**Table 4: Frequency of Adverse Reactions in Elevated LDL-C Patients**

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| Infections and infestations | Uncommon | Gastroenteritis<br>Gastrointestinal infection<br>Influenza<br>Nasopharyngitis<br>Sinusitis |
| Blood and lymphatic system disorders | Uncommon | Anaemia |
| Metabolism and nutrition disorders | Common | Decreased appetite |
| | Uncommon | Dehydration<br>Increased appetite |
| Nervous system disorders | Uncommon | Paraesthesia<br>Somnolence |
| Eye disorders | Uncommon | Eye swelling |
| Ear and labyrinth disorders | Uncommon | Vertigo |
| Respiratory, thoracic and mediastinal disorders | Uncommon | Pharyngeal lesion<br>Upper-airway cough syndrome |
| Gastrointestinal disorders | Very common | Diarrhoea<br>Nausea<br>Flatulence |
| | Common | Abdominal pain upper<br>Abdominal distension<br>Abdominal pain<br>Vomiting<br>Abdominal discomfort<br>Dyspepsia<br>Eructation<br>Abdominal pain lower<br>Frequent bowel movements |
| | Uncommon | Dry mouth<br>Faeces hard<br>Gastrooeosophageal reflux disease<br>Abdominal tenderness<br>Epigastric discomfort<br>Gastric dilatation<br>Haematemesis<br>Lower gastrointestinal haemorrhage<br>Reflux oesophagitis |
| Hepatobiliary disorders | Uncommon | Hepatomegaly |
| Skin and subcutaneous tissue disorders | Uncommon | Blister<br>Dry skin<br>Hyperhidrosis |
| Musculoskeletal and connective tissue disorders | Common | Muscle spasms |
| | Uncommon | Arthralgia<br>Myalgia<br>Pain in extremity<br>Joint swelling<br>Muscle twitching |
| Renal and urinary disorders | Uncommon | Haematuria |

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| General disorders and administrative site conditions | Common | Fatigue<br>Asthenia |
| | Uncommon | Chest pain<br>Chills<br>Early satiety<br>Gait disturbance<br>Malaise<br>Pyrexia |
| Investigations | Common | Alanine aminotransferase increased<br>Aspartate aminotransferase increased<br>Hepatic enzyme increased<br>Liver function test abnormal<br>Neutrophil count decreased<br>White blood cell count decreased |
| | Uncommon | Weight decreased<br>Blood bilirubin increased<br>Gamma-glutamyltransferase increased<br>Neutrophil percentage increased<br>Protein urine<br>Prothrombin time prolonged<br>Pulmonary function test abnormal<br>White blood cell count increased |

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

There is no specific treatment in the event of overdose. In rodents, single oral doses of lomitapide ≥600 times higher than the maximum recommended human dose (1 mg/kg) were well tolerated. The maximum dose administered to human subjects in clinical studies was 200 mg as a single dose; there were no adverse reactions.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other lipid modifying agents, plain. ATC code: C10AX12

Mechanism of action

Lomitapide is a selective inhibitor of microsomal 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 reduces lipoprotein secretion and circulating concentrations of lipoprotein-borne lipids including cholesterol and triglycerides.

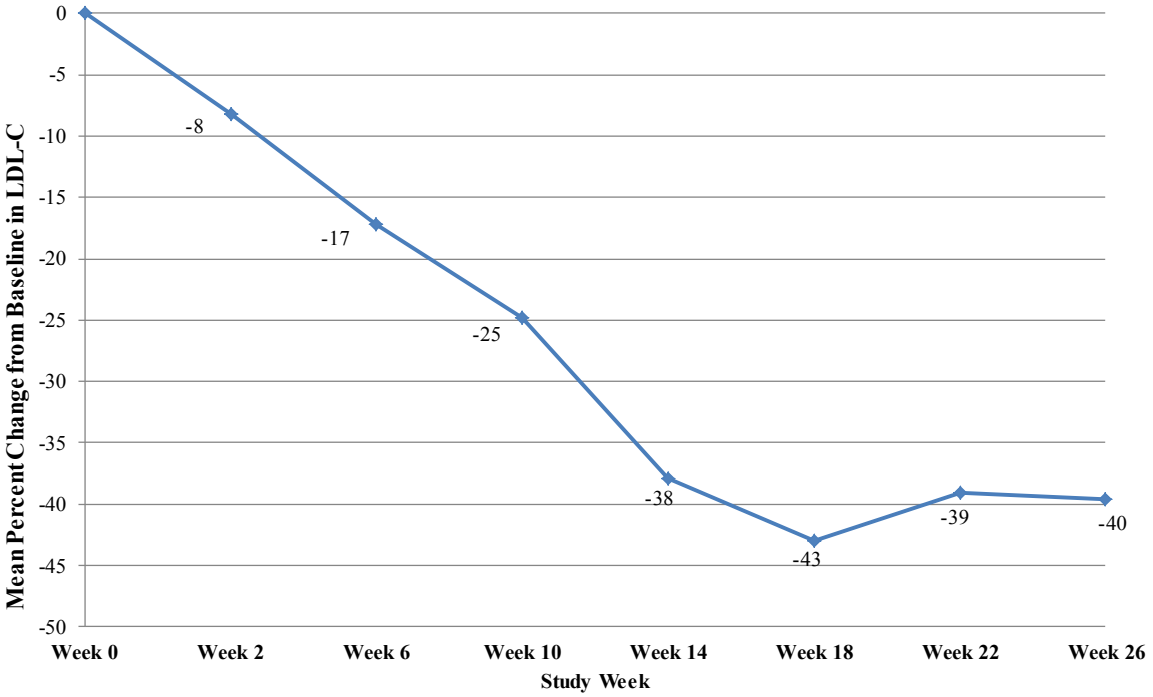
Clinical efficacy and safety

A single arm, open-label study (UP1002/AEGR-733-005) evaluated the efficacy and safety of lomitapide when co-administered with a low-fat diet and other lipid-lowering therapies in adult

patients with HoFH. Patients were instructed to maintain a low-fat diet (<20% calories from fat) and their lipid-lowering therapies at study entry, including apheresis if applicable, from 6 weeks prior to baseline through at least Week 26. The dose of lomitapide was escalated from 5 mg to an individually determined maximum tolerated dose up to 60 mg. After Week 26, patients remained on lomitapide to determine the effects of longer-term treatment and were allowed to change background lipid-lowering therapies. The study provided for a total of 78 weeks of treatment.

Twenty-nine patients were enrolled, of whom 23 completed through Week 78. Sixteen males (55%) and 13 females (45%) were included with a mean age of 30.7 years, ranging from 18 to 55 years. The mean dose of lomitapide was 45 mg at Week 26 and 40 mg at Week 78. At Week 26, the mean percent change in LDL-C from baseline of LDL-C was -40% ($p<0.001$) in the Intent to Treat (ITT) population. Mean percent change from baseline through Week 26 using last observation carried forward (LOCF) to each assessment is shown in Figure 1.

**Figure 1: Mean percent changes from baseline in LDL-C in the major effectiveness study UP1002/AEGR-733-005 through Week 26 (the Primary Endpoint) using LOCF to each assessment (N=29)**




Changes in lipids and lipoproteins through Week 26 and Week 78 of lomitapide treatment are presented in Table 5.

**Table 5: Absolute values and percent changes from baseline to Weeks 26 and 78 in lipids and lipoproteins (major effectiveness study UP1002/AEGR-733-005)**

| Parameter (units) | Baseline | Week 26/LOCF (N=29) | | | Week 78 (N=23) | | |
|---|---|---|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | % Change | p-value[b] | Mean (SD) | % Change | p-value[b] |
| LDL-C, direct (mg/dL) | 336 (114) | 190 (104) | -40 | <0.001 | 210 (132) | -38 | <0.001 |
| Total Cholesterol (TC) (mg/dL) | 430 (135) | 258 (118) | -36 | <0.001 | 281 (149) | -35 | <0.001 |
| Apolipoprotein B (apo B) (mg/dL) | 259 (80) | 148 (74) | -39 | <0.001 | 151 (89) | -43 | <0.001 |
| Triglycerides (TG) (mg/dL)[a] | 92 | 57 | -45 | 0.009 | 59 | -42 | 0.012 |
| Non high-density lipoprotein cholesterol (Non-HDL-C) (mg/dL) | 386 (132) | 217 (113) | -40 | <0.001 | 239 (146) | -39 | <0.001 |
| Very-low-density lipoprotein cholesterol (VLDL-C) (mg/dL) | 21 (10) | 13 (9) | -29 | 0.012 | 16 (15) | -31 | 0.013 |
| Lipoprotein (a) (Lp(a)) (nmol/L)[a] | 66 | 61 | -13 | 0.094 | 72 | -4 | <0.842 |
| High-density lipoprotein cholesterol (HDL-C) (mg/dL) | 44 (11) | 41 (13) | -7 | 0.072 | 43 (12) | -4.6 | 0.246 |

[a] Median presented for TG and Lp(a). p-value is based on the mean percent change
[b] p-value on the mean percent change from baseline based on paired t-test

At both Week 26 and Week 78, there were significant reductions in LDL-C, TC, apo B, TG, non-HDL-C, VLDL-C and changes in HDL-C trended lower at Week 26 and returned to baseline levels by Week 78.

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

At baseline, 93% were on a statin, 76% were on ezetimibe, 10% on niacin, 3% on a bile acid sequestrant and 62% were receiving apheresis. Fifteen of 23 (65%) patients had their lipid-lowering treatment reduced by Week 78, including planned and unplanned reductions/interruptions. Apheresis was discontinued in 3 out of 13 patients who were on it at Week 26, and frequency was reduced in 3 patients while maintaining low LDL-C levels through Week 78. The clinical benefit of reductions in background lipid-lowering therapy, including apheresis, is not certain.

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 and 1 having LDL-C <70 mg/dL at that time point.

In this study, 10 patients experienced elevations in AST and/or ALT >3 x ULN (see Table 6).

**Table 6: Highest liver function test results post first dose (major effectiveness study UP1002/AEGR-733-005)**

| **Parameter/Abnormality** | **N (%)** |
|---|---|
| ALT | |
| Number of Patients with Assessments | 29 |
| >3 to ≤5 x ULN | 6 (20.7) |
| >5 to ≤10 x ULN | 3 (10.3) |
| >10 to ≤20 x ULN | 1 (3.4) |
| >20 x ULN | 0 |
| AST | |
| Number of Patients with Assessments | 29 |
| >3 to ≤5 x ULN | 5 (17.2) |
| >5 to ≤10 x ULN | 1 (3.4) |
| >10 to ≤20 x ULN | 0 |
| >20 x ULN | 0 |

Elevations in ALT and/or AST >5 x ULN were managed with a dose reduction or temporary suspension of lomitapide dosing, and all patients were able to continue with study drug treatment. No clinically meaningful elevations in total bilirubin or alkaline phosphatase were observed. Hepatic fat was prospectively measured using MRS in all eligible patients during the clinical trial (Table 7). Data from individuals who had repeat measurements after stopping lomitapide show that hepatic fat accumulation is reversible, but whether histological sequelae remain is unknown.

**Table 7: Maximum categorical changes in % hepatic fat (major effectiveness study UP1002/AEGR-733-005)**

| **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) |

The European Medicines Agency has deferred the obligation to submit the results of studies with Lojuxta in one or more subsets of the paediatric population in HoFH (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption

The absolute oral bioavailability of lomitapide is 7%. Absorption is not limited by penetration of the drug across the intestinal barrier but is predominantly influenced by an extensive first pass effect. Peak plasma concentrations of lomitapide were reached 4-8 hours following oral dosing. Lomitapide pharmacokinetics is approximately dose-proportional for oral single doses in the therapeutic range. Doses higher than 60 mg suggest a trend toward nonlinearity and are not recommended.

Upon multiple dosing $C_{max}$ and AUC increased in approximate proportion to lomitapide dose. $C_{max}$ and AUC were increased following either a high-fat meal (77% and 58%, respectively) or low fat meal (70% and 28%, respectively). Accumulation of lomitapide in plasma was consistent with that predicted after a single dose following once daily oral dosing above 25 mg for up to 4 weeks. Inter-individual variability in lomitapide AUC was approximately 50%.

At steady state the accumulation of lomitapide was 2.7 at 25 mg and 3.9 at 50 mg.

Distribution

Following intravenous administration, the volume of distribution of lomitapide was high (mean=1200 litres) despite a high degree (>99.8%) of binding to plasma protein. In animal studies lomitapide was highly concentrated (200-fold) in the liver.

Biotransformation

Lomitapide is extensively metabolised, predominantly by CYP3A4. CYP isoforms 2E1, 1A2, 2B6, 2C8, and 2C19 are involved to a lesser extent and isoforms 2D6 and 2C9 are not involved in the metabolism of lomitapide.

Elimination

Following administration of a radiolabeled oral solution dose to healthy subjects, 93% of the administered dose was recovered in urine and faeces. Approximately 33% of the radioactivity was excreted in urine as metabolites. The remainder was excreted in faeces, primarily as oxidised metabolites. The elimination half-life of lomitapide was approximately 29 hours.

Special populations

Data in the pivotal clinical trial were analyzed with respect to the impact of potential covariates on lomitapide exposure. Of the parameters examined (race, body mass index (BMI), gender, weight, age), only BMI could be classified as a potential covariate.

*Age and gender*

There was no clinically relevant effect of age (18-64 years) or gender on the pharmacokinetics of lomitapide.

*Race*

No dose adjustment is required for Caucasian or Latino patients. There is insufficient information to determine if Lojuxta requires dose adjustment in other races. However, since the medicinal product is dosed in an escalating fashion according to individual patient safety and tolerability, no adjustment to the dosing regimen is recommended based on race.

*Renal insufficiency*

In the renal impairment population, lomitapide was only studied in patients with end-stage renal disease (ESRD). A pharmacokinetic study in patients with ESRD undergoing hemodialysis demonstrated a 36% increase in mean lomitapide plasma concentration compared to matched healthy controls. The terminal half-life of lomitapide was not affected.

*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. Lojuxta has not been studied in patients with severe hepatic impairment (Child-Pugh score 10-15).

*Paediatric population*

Lojuxta has not been investigated in children less than 18 years of age.

*Elderly population*

Lojuxta has not been investigated in patients aged 65 years or older.

## 5.3 Preclinical safety data

In repeat-dose oral toxicology studies in rodents and dogs, the principal drug-related findings were lipid accumulation in the small intestine and/or liver associated with decreases in serum cholesterol and/or triglyceride levels. These changes are secondary to the mechanism of action of lomitapide. Other liver-related changes in repeat-dose toxicity studies in rats and dogs included increased serum aminotransferases, subacute inflammation (rats only), and single-cell necrosis. In a 1 year repeat-dose study in dogs there were no microscopic changes in the liver although serum AST was minimally increased in females.

Pulmonary histiocytosis was observed in rodents. Decreased red blood cell parameters as well as poikilocytosis and/or anisocytosis were observed in dogs. Testicular toxicity was observed in dogs at 205 times the human exposure (AUC) at 60 mg in a 6-month study. No adverse effects on the testes were observed in a 1-year study in dogs at 64 times the human exposure at 60 mg.

In a dietary carcinogenicity study in mice, lomitapide was administered up to 104 weeks at doses ranging from 0.3 to 45 mg/kg/day. There were statistically significant increases in the incidences of liver adenoma and carcinoma at doses ≥1.5 mg/kg/day in males (≥ 2 times the human exposure at 60 mg daily based on AUC) and ≥7.5 mg/kg/day in females (≥ 9 times the human exposure at 60 mg based on AUC). Incidences of small intestinal carcinoma and/or combined adenoma and carcinoma (rare tumours in mice) were significantly increased at doses ≥15 mg/kg/day in males (≥ 26 times the human exposure at 60 mg based on AUC) and at 15 mg/kg/day in females (22 times the human exposure at 60 mg based on AUC).

In an oral carcinogenicity study in rats, lomitapide was administered up to 99 weeks at doses up to 7.5 mg/kg/day in males and 2.0 mg/kg/day in females. Focal hepatic fibrosis was observed in males and females and hepatic cystic degeneration was observed in males only. In high-dose males, an increased incidence of pancreatic acinar cell adenoma was observed at an exposure 6 times that in humans at 60 mg based on AUC.

Lomitapide was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* studies.

Lomitapide had no effect on reproductive function in female rats at doses up to 1 mg/kg or in male rats at doses up to 5 mg/kg. Systemic exposures to lomitapide at these doses were estimated to be 4 times (females) and 5 times (males) higher than the human exposure at 60 mg based on AUC.

Lomitapide was teratogenic in rats in the absence of maternal toxicity at an exposure (AUC) estimated to be twice that in humans at 60 mg. There was no evidence of embryofoetal toxicity in rabbits at 3 times the maximum recommended human dose (MRHD) of 60 mg based on body surface area. Embryofoetal toxicity was observed in rabbits in the absence of maternal toxicity at ≥6.5 times the MRHD. In ferrets, lomitapide was both maternally toxic and teratogenic at <1 times the MRHD.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule content
Pregelatinised starch (maize)
Sodium starch glycolate
Microcrystalline cellulose
Lactose monohydrate
Silica, colloidal anhydrous
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)

Printing ink
Shellac
Black iron oxide (E172)
Propylene glycol

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years.

### 6.4 Special precautions for storage

Store below 30°C.
Keep the bottle tightly closed in order to protect from moisture.

### 6.5 Nature and contents of container

High density polyethylene (HDPE) bottle fitted with a polyester/aluminium foil/cardboard induction seal and polypropylene screw cap.

Package sizes are:
28 capsules

### 6.6 Special precautions for disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Aegerion Pharmaceuticals Ltd
Lakeside House
1 Furzeground Way
Stockley Park East
Uxbridge UB11 1BD
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/851/002

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 July 2013

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Lojuxta 20 mg hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains lomitapide mesylate equivalent to 20 mg lomitapide.

Excipient with known effect
Each hard capsule contains 129.89 mg of lactose (as monohydrate) (see section 4.4).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Capsule, hard.

The capsule is a white cap/white body hard capsule of 19.4 mm, printed with black ink imprinted with "20 mg" on body and "A733" on cap.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Lojuxta is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH).

Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism) must be excluded.

### 4.2 Posology and method of administration

Treatment with Lojuxta should be initiated and monitored by a physician experienced in the treatment of lipid disorders.

Posology

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 to the maximum recommended dose of 60 mg (see section 4.8).

The dose should be escalated gradually to minimise the incidence and severity of gastrointestinal side effects and aminotransferase elevations.

Administration with food may increase exposure to Lojuxta. Lojuxta should be taken on an empty stomach, at least 2 hours after the evening meal because the fat content of a recent meal may adversely impact gastrointestinal tolerability.

The occurrence and severity of gastrointestinal adverse reactions associated with the use of Lojuxta decreases in the presence of a low fat diet. Patients should follow a diet supplying less than 20% of energy from fat prior to initiating Lojuxta treatment, and should continue this diet during treatment. Dietary counselling should be provided.

Patients should avoid consumption of grapefruit juice (see sections 4.4 and 4.5).

For patients on a stable maintenance dose of Lojuxta who receive atorvastatin either:

- Separate the dose of the medications by 12 hours

OR

- Decrease the dose of Lojuxta by half.

Patients on 5 mg should remain on 5 mg.
Careful titration may then be considered according to LDL-C response and safety/tolerability.
Upon discontinuation of atorvastatin the dose of Lojuxta should be up-titrated according to LDL-C response and safety/tolerability.

For patients on a stable maintenance dose of Lojuxta who receive any other weak CYP3A4 inhibitor, separate the dose of the medications (Lojuxta and the weak CYP3A4 inhibitor) by 12 hours.

Consider limiting the maximum dose of Lojuxta according to desired LDL-C response.
Exercise additional caution if administering more than 1 weak CYP3A4 inhibitor with Lojuxta.

Based on observations of decreased essential fatty acid and vitamin E levels in clinical trials, patients should take daily dietary supplements that provide 400 IU vitamin E and approximately 200 mg linoleic acid, 110 mg eicosapentaenoic acid (EPA), 210 mg alpha linolenic acid (ALA) and 80 mg docosahexaenoic acid (DHA) per day, throughout treatment with Lojuxta.

*Elderly population*

There is limited experience with Lojuxta in patients aged 65 years or older. Therefore, particular caution should be exercised in these patients.

Since the recommended dose regimen involves starting at the low end of the dosing range and escalating cautiously according to individual patient tolerability, no adjustment to the dosing regimen is recommended for the elderly.

*Hepatic impairment*

Lojuxta is contraindicated in patients with moderate or severe hepatic impairment including patients with unexplained persistent abnormal liver function tests (see section 5.2).

Patients with mild hepatic impairment (Child-Pugh A) should not exceed 40 mg daily.

*Renal impairment*

Patients with end-stage renal disease receiving dialysis should not exceed 40 mg daily (see section 5.2).

*Paediatric population*

The safety and efficacy of Lojuxta in children < 18 years have not been established and the use of this medicinal product in children is therefore not recommended. No data are available.

Method of administration

Oral use.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests.
- Patients with a known significant or chronic bowel disease such as inflammatory bowel disease or malabsorption.
- Concomitant administration of >40 mg simvastatin (see section 4.5).
- Concomitant use of Lojuxta with strong or moderate cytochrome P450 (CYP) 3A4 inhibitors (e.g., antifungal azoles such as itraconazole, fluconazole,ketoconazole, voriconazole, posaconazole; macrolide antibiotics such as erythromycin or clarithromycin; ketolide antibiotics such as telithromycin; HIV protease inhibitors; the calcium channel blockers diltiazem and verapamil, and the anti-arrhythmic dronedarone [see section 4.5]).
- Pregnancy (see section 4.6).

## 4.4 Special warnings and precautions for use

Liver enzyme abnormalities and liver monitoring

Lomitapide can cause elevations in alanine aminotransferase [ALT] and aspartate aminotransferase [AST] and hepatic steatosis. The extent to which lomitapide-associated hepatic steatosis promotes the elevations in aminotransferase is unknown. Although cases of hepatic dysfunction (elevated aminotransferase with increase in bilirubin or International Normalized Ratio [INR]) or hepatic failure have not been reported, there is concern that lomitapide could induce steatohepatitis, which can progress to cirrhosis over several years. The clinical studies supporting the safety and efficacy of lomitapide in HoFH would have been unlikely to detect this adverse outcome given their size and duration.

Elevations in aminotransferases (ALT and/or AST) are associated with lomitapide (see section 5.1). There were no concomitant or subsequent clinically meaningful elevations in serum bilirubin, INR, or alkaline phosphatase. Liver enzyme changes occur most often during dose escalation, but may occur at any time during therapy.

Monitoring of liver function tests

Measure ALT, AST, alkaline phosphatase, total bilirubin, gamma-glutamyl transferase (gamma-GT) and serum albumin before initiation of treatment with Lojuxta. The medicinal product is contraindicated in patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests. If the baseline liver-related tests are abnormal, consider initiating the medicinal product after appropriate investigation by a hepatologist and the baseline abnormalities are explained or resolved.

During the first year, measure liver-related tests (ALT and AST, at a minimum) prior to each increase in dose or monthly, whichever occurs first. After the first year, do these tests at least every 3 months and before any increase in dose. Decrease the dose of Lojuxta if elevations of aminotransferase are observed and discontinue treatment for persistent or clinically significant elevations (see Table 1 for specific recommendations).

Dose modification based on elevated hepatic aminotransferases

Table 1 summarizes recommendations for dose adjustment and monitoring for patients who develop elevated aminotransferase during therapy with Lojuxta.

**Table 1: Dose Adjustment and Monitoring for Patients with Elevated Aminotransferases**

| ALT or AST | Treatment and monitoring recommendations* |
|---|---|
| ≥3x and <5x Upper Limit of Normal (ULN) | • Confirm elevation with a repeat measurement within one week.<br>• If confirmed, reduce the dose and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR).<br>• Repeat tests weekly and withhold dosing if there are signs of abnormal liver function (increase in bilirubin or INR), if aminotransferase levels rise above 5x ULN, or if aminotransferase levels do not fall below 3x ULN within approximately 4 weeks. Refer patients with persistent elevations in aminotransferase >3x ULN to a hepatologist for further investigation.<br>• If resuming Lojuxta after aminotransferase levels resolve to <3x ULN, consider reducing the dose and monitor liver-related tests more frequently. |
| ≥5x ULN | • Withhold dosing and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR). If aminotransferase levels do not fall below 3x ULN within approximately 4 weeks refer the patient to a hepatologist for further investigation.<br>• If resuming Lojuxta after aminotransferase levels 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 aminotransferase 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 Lojuxta and refer the patient to a hepatologist for further investigation.

Reintroduction of treatment may be considered if the benefits are considered to outweigh the risks associated with potential liver disease.

Hepatic steatosis and risk of progressive liver disease

Consistent with the mechanism of action of lomitapide, most treated patients exhibited increases in hepatic fat content. In an open-label Phase 3 study, 18 of 23 patients with HoFH developed hepatic steatosis (hepatic fat >5.56%) as measured by nuclear magnetic resonance spectroscopy (MRS) (see section 5.1). The median absolute increase in hepatic fat was 6% after both 26 weeks and 78 weeks of treatment, from 1% at baseline, measured by MRS. Hepatic steatosis is a risk factor for progressive liver disease including steatohepatitis and cirrhosis. The long term consequences of hepatic steatosis associated with Lojuxta treatment are unknown. Clinical data suggest that hepatic fat accumulation is reversible after stopping treatment with Lojuxta, but whether histological sequelae remain is unknown, especially after long-term use.

Monitoring for evidence of progressive liver disease.

Regular screening for steatohepatitis/fibrosis should be performed at baseline and on an annual basis using the following imaging and biomarker evaluations:

- Imaging for tissue elasticity, e.g. Fibroscan, acoustic radiation force impulse (ARFI), or magnetic resonance (MR) elastography

- Gamma-GT and serum albumin to detect possible liver injury

- At least one marker from each of the following categories:

    - High sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), CK-18 Fragment, NashTest (liver inflammation)
    - Enhanced Liver Fibrosis (ELF) panel, Fibrometer, AST/ALT ratio, Fib-4 score, Fibrotest (liver fibrosis)

The performance of these tests and their interpretation should involve collaboration between the treating physician and the hepatologist. Patients with results suggesting the presence of steatohepatitis or fibrosis should be considered for liver biopsy.

If a patient has biopsy-proven steatohepatitis or fibrosis, the benefit-risk should be reassessed and treatment stopped if necessary.

Dehydration

Post-marketing reports of dehydration and hospitalisation in patients treated with lomitapide have been reported. Patients treated with lomitapide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Concomitant use of CYP3A4 inhibitors

Lomitapide appears to be a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with Lojuxta is contraindicated (see section 4.3). In the lomitapide clinical trials, one patient with HoFH developed markedly elevated aminotransferase (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, Lojuxta should be stopped during the course of treatment.

Weak CYP3A4 inhibitors are expected to increase the exposure of lomitapide when taken simultaneously. When administered with atorvastatin, the dose of Lojuxta should either be taken 12 hours apart or be decreased by half (see section 4.2). The dose of Lojuxta should be administered 12 hours apart from any other weak CYP3A4 inhibitor.

Concomitant use of CYP3A4 inducers

Medicines that induce CYP3A4 would be expected to increase the rate and extent of metabolism of lomitapide. CYP3A4 inducers exert their effect in a time-dependent manner, and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2 weeks to decline.

Co-administration of a CYP3A4 inducer is expected to reduce the effect of Lojuxta. Any impact on efficacy is likely to be variable. When co-administering CYP3A4 inducers (i.e. aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, glucocorticoids, modafinil and phenytoin) with Lojuxta, the possibility of a drug-drug interaction affecting efficacy should be considered. The use of St. John’s Wort should be avoided with Lojuxta.

It is recommended to increase the frequency of LDL-C assessment during such concomitant use and consider increasing the dose of Lojuxta to ensure maintenance of the desired level of efficacy if the CYP3A4 inducer is intended for chronic use. On withdrawal of a CYP3A4 inducer, the possibility of increased exposure should be considered and a reduction in the dose of Lojuxta may be necessary.

Concomitant use of HMG-CoA reductase inhibitors ('statins')

Lomitapide increases plasma concentrations of statins. Patients receiving Lojuxta as adjunctive therapy to a statin should be monitored for adverse events that are associated with the use of high doses of statins. Statins occasionally cause myopathy. In rare cases, myopathy may take the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and can lead to fatality. All patients receiving Lojuxta in addition to a statin should be advised of the potential increased risk of myopathy and told to report promptly any unexplained muscle pain, tenderness, or weakness. Doses of simvastatin >40 mg should not be used with Lojuxta (see section 4.3).

Grapefruit juice

Grapefruit juice must be omitted from the diet while patients are treated with Lojuxta.

Risk of supratherapeutic or subtherapeutic anticoagulation with coumarin based anticoagulants

Lomitapide increases the plasma concentrations of warfarin. Increases in the dose of Lojuxta may lead to supratherapeutic anticoagulation, and decreases in the dose may lead to subtherapeutic anticoagulation. Difficulty controlling INR contributed to early discontinuation from the Phase 3 trial for one of five patients taking concomitant warfarin. Patients taking warfarin should undergo regular monitoring of the INR, especially after any changes in Lojuxta dosage. The dose of warfarin should be adjusted as clinically indicated.

Use of alcohol

Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. In the Phase 3 trial, 3 of 4 patients with ALT elevations >5x ULN reported alcohol consumption beyond the limits recommended in the protocol. The use of alcohol during Lojuxta treatment is not recommended.

Hepatotoxic agents

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

Reduced absorption of fat-soluble vitamins and serum fatty acids

Given its mechanism of action in the small intestine, lomitapide may reduce the absorption of fat-soluble nutrients. In the Phase 3 trial, patients were provided daily dietary supplements of vitamin E, linoleic acid, ALA, EPA and 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 lomitapide treatment of up to 78 weeks. Patients treated with Lojuxta should take daily supplements that contain 400 international units vitamin E and approximately 200 mg linoleic acid, 210 mg ALA, 110 mg EPA, and 80 mg DHA.

Contraception measures in women of child-bearing potential

Before initiating treatment in women of child-bearing potential, appropriate advice on effective methods of contraception should be provided, and effective contraception initiated. Patients taking oestrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting (see section 4.5). Oestrogen-containing oral contraceptives are weak CYP3A4 inhibitors (see section 4.2).

Patients should be advised to immediately contact their physician and stop taking Lojuxta if they become pregnant (see section 4.6).

Lactose

Lojuxta contains lactose and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption.

## 4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on Lojuxta and other forms of interaction

**Table 2: Interactions between Lojuxta and other medicinal products and other forms of interaction**

| Medicinal products | Effects on lomitapide levels | Recommendation concerning co-administration with Lojuxta |
|---|---|---|
| Inhibitors of CYP3A4 | When lomitapide 60 mg was co-administered with ketoconazole 200 mg twice daily, a strong inhibitor of CYP3A4, lomitapide AUC increased approximately 27-fold and $C_{max}$ increased approximately 15-fold.<br><br>Interactions between moderate CYP3A4 inhibitors and lomitapide have not been studied.<br><br>Moderate CYP3A4 inhibitors are predicted to have a substantial impact on lomitapide's pharmacokinetics. Concomitant use of moderate CYP3A4 inhibitors are expected to increase lomitapide exposure by 4-10 fold based on the results of the study with the strong CYP3A4 inhibitor ketoconazole and on historical data for the model CYP3A4 probe midazolam.<br><br>Weak CYP3A4 inhibitors are expected to increase the exposure of lomitapide when taken simultaneously.<br><br>When lomitapide 20 mg was co-administered simultaneously with atorvastatin, a weak CYP3A4 inhibitor, lomitapide AUC and $C_{max}$ increased approximately 2-fold. When the dose of lomitapide was taken 12 hours apart from atorvastatin, | Use of strong or moderate inhibitors of CYP3A4 is contraindicated with Lojuxta. If treatment with antifungal azoles (e.g., itraconazole, ketoconazole, fluconazole, voriconazole, posaconazole); the antiarrhythmic dronedarone; macrolide antibiotics (e.g., erythromycin, clarithromycin); ketolide antibiotics (e.g., telithromycin); HIV protease inhibitors; the calcium channel blockers diltiazem and verapamil is unavoidable, therapy with Lojuxta should be suspended during the course of treatment (see sections 4.3 and 4.4).<br><br>Grapefruit juice is a moderate inhibitor of CYP3A4 and is expected to substantially increase exposure to lomitapide. Patients taking Lojuxta should avoid consumption of grapefruit juice.<br><br>When administered with atorvastatin, the dose of Lojuxta should either be taken 12 hours apart or be decreased by half (see section 4.2). The dose of Lojuxta should be taken 12 hours apart from any other concomitant weak CYP3A4 inhibitors. Examples of weak CYP3A4 inhibitors include: alprazolam, amiodarone, amlodipine, atorvastatin, azithromycin, bicalutamide, cilostazol, cimetidine, ciclosporin, clotrimazole, fluoxetine, fluvoxamine, fosaprepitant, ginkgo, goldenseal, isoniazid, ivacaftor, lacidipine, lapatinib, linagliptin, nilotinib, oestrogen-containing oral contraceptives, pazopanib, peppermint oil, propiverine, ranitidine, ranolazine, roxithromycin, Seville oranges, tacrolimus, ticagrelor and tolvaptan. This |

| Medicinal products | Effects on lomitapide levels | Recommendation concerning co-administration with Lojuxta |
|---|---|---|
| | no clinically meaningful increase in lomitapide exposure was observed.<br><br>When lomitapide 20 mg was co-administered simultaneously or 12 hours apart with ethinyl estradiol/norgestimate, a weak CYP3A4 inhibitor, no clinically meaningful increase in lomitapide exposure was observed. | list is not intended to be comprehensive and prescribers should check the prescribing information of drugs to be co-administered with Lojuxta for potential CYP3A4 mediated interactions.<br><br>The effect of administration of more than one weak CYP3A4 inhibitor has not been tested, but the effect on the exposure of lomitapide is expected to be greater than for co-administration of the individual inhibitors with lomitapide.<br><br>Exercise additional caution if administering more than 1 weak CYP3A4 inhibitor with Lojuxta. |
| Inducers of CYP3A4 | Medicines that induce CYP3A4 would be expected to increase the rate and extent of metabolism of lomitapide. Consequently, this would reduce the effect of lomitapide. Any impact on efficacy is likely to be variable. | When co-administering CYP3A4 inducers (i.e., aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, St John's Wort, glucocorticoids, modafinil and phenytoin) with Lojuxta, the possibility of a drug-drug interaction affecting efficacy should be considered. It is recommended to increase the frequency of LDL-C assessment during such concomitant use and consider increasing the dose of Lojuxta to ensure maintenance of the desired level of efficacy if the CYP3A4 inducer is intended for chronic use. |
| Bile acid sequestrants | Lomitapide has not been tested for interaction with bile acid sequestrants (resins such as colesevelam and cholestyramine). | Because bile acid sequestrants can interfere with the absorption of oral medicines, bile acid sequestrants should be taken at least 4 hours before or at least 4 hours after Lojuxta. |

Effects of lomitapide on other medicinal products

*HMG-CoA Reductase Inhibitors ("Statins"):* Lomitapide increases plasma concentrations of statins. When lomitapide 60 mg was administered to steady state prior to simvastatin 40 mg, simvastatin acid AUC and $C_{max}$ increased 68% and 57%, respectively. When lomitapide 60 mg was administered to steady state prior to atorvastatin 20 mg, atorvastatin acid AUC and $C_{max}$ increased 52% and 63%, respectively. When lomitapide 60 mg was administered to steady state prior to rosuvastatin 20 mg, rosuvastatin $T_{max}$ increased from 1 to 4 hours, AUC was increased 32%, and its $C_{max}$ was unchanged. The risk of myopathy with simvastatin is dose related. Use of Lojuxta is contraindicated in patients treated with high doses of simvastatin (>40 mg) (see sections 4.3 and 4.4).

*Coumarin anticoagulants:* When lomitapide 60 mg was administered to steady state and 6 days following warfarin 10 mg, INR increased 1.26-fold. AUCs for R(+)-warfarin and S(-)-warfarin increased 25% and 30%, respectively. $C_{max}$ for R(+)-warfarin and S(-)-warfarin increased 14% and 15%, respectively. In patients taking coumarins (such as warfarin) and Lojuxta concomitantly, INR

should be determined before starting Lojuxta and monitored regularly with dosage of coumarins adjusted as clinically indicated (see section 4.4).

*Fenofibrate, niacin and ezetimibe*: When lomitapide was administered to steady state prior to micronised fenofibrate 145 mg, extended release niacin 1000 mg, or ezetimibe 10 mg, no clinically significant effects on the exposure of any of these medicinal products were observed. No dose adjustments are required when co-administered with Lojuxta.

*Oral contraceptives:* When lomitapide 50 mg was administered to steady state along with an oestrogen-based oral contraceptive, no clinically meaningful or statistically significant impact on the pharmacokinetics of the components of the oral contraceptive (ethinyl estradiol and 17-deacetyl norgestimate, the metabolite of norgestimate) was observed. Lomitapide is not expected to directly influence the efficacy of oestrogen based oral contraceptives; however diarrhoea and/or vomiting may reduce hormone absorption. In cases of protracted or severe diarrhoea and/or vomiting lasting more than 2 days, additional contraceptive measures should be used for 7 days after resolution of symptoms.

*P-gp substrates:* Lomitapide inhibits P-gp *in vitro*, and may increase the absorption of P-gp substrates. Coadministration of Lojuxta 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 Lojuxta.

*In vitro assessment of drug interactions*: Lomitapide inhibits CYP3A4. Lomitapide does not induce CYPs 1A2, 3A4, or 2B6, and does not inhibit CYPs 1A2, 2B6, 2C9, 2C19, 2D6, or 2E1. Lomitapide is not a P-gp substrate but does inhibit P-gp. Lomitapide does not inhibit breast cancer resistance protein (BCRP).

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Lojuxta is contraindicated during pregnancy. There are no reliable data on its use in pregnant women. Animal studies have shown developmental toxicity (teratogenicity, embryotoxicity, see section 5.3). The potential risk for humans is unknown.

Use in women of child-bearing potential

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. Patients taking oestrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting. Additional contraceptive measures should be used until resolution of symptoms (see section 4.5).

Breast-feeding

It is not known whether lomitapide is excreted into human milk. Because of the potential for adverse effects based on findings in animal studies with lomitapide (see section 5.3), a decision should be made whether to discontinue breast-feeding or discontinue the medicinal product, taking into account the importance of the medicinal product to the mother.

Fertility

No adverse effects on fertility were observed in male and female rats administered lomitapide at systemic exposures (AUC) estimated to be 4 to 5 times higher than in humans at the maximum recommended human dose (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Lojuxta may have a minor influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile

The most serious adverse reactions during treatment were liver aminotransferase abnormalities (see section 4.4).

The most common adverse reactions were gastrointestinal effects. Gastrointestinal adverse reactions were reported by 27 (93%) of 29 patients in the Phase 3 clinical trial. Diarrhoea 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. Gastrointestinal adverse reactions occurred more frequently during the dose escalation phase of the study and decreased once patients established the maximum tolerated dose of lomitapide.

Gastrointestinal adverse reactions of severe intensity were reported by 6 (21%) of 29 patients in the Phase 3 clinical trial, with the most common being diarrhoea (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.

The most commonly reported adverse reactions of severe intensity were diarrhoea (4 subjects, 14%), vomiting (3 patients, 10%), and abdominal distension and ALT increased (2 subjects each, 7%).

Tabulated list of adverse reactions

Frequency of the adverse reactions is defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 3 lists all adverse reactions reported across the 35 patients treated in the Phase 2 Study UP1001 and in the Phase 3 Study UP1002/AEGR-733-005 or its extension study AEGR-733-012.

**Table 3: Frequency of Adverse Reactions in HoFH Patients**

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| Infections and infestations | Common | Gastroenteritis |
| Metabolism and nutrition disorders | Very common | Decreased appetite |
| | Not known | Dehydration |
| Nervous system disorders | Common | Dizziness<br>Headache<br>Migraine |
| Gastrointestinal disorders | Very common | Diarrhoea<br>Nausea<br>Vomiting<br>Abdominal discomfort<br>Dyspepsia<br>Abdominal pain<br>Abdominal pain upper<br>Flatulence<br>Abdominal distension<br>Constipation |
| | Common | Gastritis<br>Rectal tenesmus<br>Aerophagia<br>Defaecation urgency<br>Eructation<br>Frequent bowel movements<br>Gastric dilatation<br>Gastric disorder<br>Gastrooesophageal reflux disease<br>Haemorrhoidal haemorrhage<br>Regurgitation |
| Hepatobiliary disorders | Common | Hepatic steatosis<br>Hepatotoxicity<br>Hepatomegaly |
| Skin and subcutaneous tissue disorders | Common | Ecchymosis<br>Papule<br>Rash erythematous<br>Xanthoma |
| | Not known | Alopecia |
| Musculoskeletal and connective tissue disorders | Not known | Myalgia |
| General disorders and administration site conditions | Common | Fatigue |
| Investigations | Very common | Alanine aminotransferase increased<br>Aspartate aminotransferase increased<br>Weight decreased |
| | Common | International normalised ratio increased<br>Blood alkaline phosphatase increased<br>Blood potassium decreased<br>Carotene decreased<br>International normalised ratio abnormal<br>Liver function test abnormal<br>Prothrombin time prolonged<br>Transaminases increased<br>Vitamin E decreased<br>Vitamin K decreased |

Table 4 lists all adverse reactions for subjects who received lomitapide monotherapy (N=291) treated in Phase 2 studies in subjects with elevated LDL-C (N=462).

**Table 4: Frequency of Adverse Reactions in Elevated LDL-C Patients**

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| Infections and infestations | Uncommon | Gastroenteritis<br>Gastrointestinal infection<br>Influenza<br>Nasopharyngitis<br>Sinusitis |
| Blood and lymphatic system disorders | Uncommon | Anaemia |
| Metabolism and nutrition disorders | Common | Decreased appetite |
| | Uncommon | Dehydration<br>Increased appetite |
| Nervous system disorders | Uncommon | Paraesthesia<br>Somnolence |
| Eye disorders | Uncommon | Eye swelling |
| Ear and labyrinth disorders | Uncommon | Vertigo |
| Respiratory, thoracic and mediastinal disorders | Uncommon | Pharyngeal lesion<br>Upper-airway cough syndrome |
| Gastrointestinal disorders | Very common | Diarrhoea<br>Nausea<br>Flatulence |
| | Common | Abdominal pain upper<br>Abdominal distension<br>Abdominal pain<br>Vomiting<br>Abdominal discomfort<br>Dyspepsia<br>Eructation<br>Abdominal pain lower<br>Frequent bowel movements |
| | Uncommon | Dry mouth<br>Faeces hard<br>Gastrooeosophageal reflux disease<br>Abdominal tenderness<br>Epigastric discomfort<br>Gastric dilatation<br>Haematemesis<br>Lower gastrointestinal haemorrhage<br>Reflux oesophagitis |
| Hepatobiliary disorders | Uncommon | Hepatomegaly |
| Skin and subcutaneous tissue disorders | Uncommon | Blister<br>Dry skin<br>Hyperhidrosis |
| Musculoskeletal and connective tissue disorders | Common | Muscle spasms |
| | Uncommon | Arthralgia<br>Myalgia<br>Pain in extremity<br>Joint swelling<br>Muscle twitching |
| Renal and urinary disorders | Uncommon | Haematuria |

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| General disorders and administrative site conditions | Common | Fatigue<br>Asthenia |
| | Uncommon | Chest pain<br>Chills<br>Early satiety<br>Gait disturbance<br>Malaise<br>Pyrexia |
| Investigations | Common | Alanine aminotransferase increased<br>Aspartate aminotransferase increased<br>Hepatic enzyme increased<br>Liver function test abnormal<br>Neutrophil count decreased<br>White blood cell count decreased |
| | Uncommon | Weight decreased<br>Blood bilirubin increased<br>Gamma-glutamyltransferase increased<br>Neutrophil percentage increased<br>Protein urine<br>Prothrombin time prolonged<br>Pulmonary function test abnormal<br>White blood cell count increased |

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

There is no specific treatment in the event of overdose. In rodents, single oral doses of lomitapide ≥600 times higher than the maximum recommended human dose (1 mg/kg) were well tolerated. The maximum dose administered to human subjects in clinical studies was 200 mg as a single dose; there were no adverse reactions.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other lipid modifying agents, plain. ATC code: C10AX12

Mechanism of action

Lomitapide is a selective inhibitor of microsomal 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 reduces lipoprotein secretion and circulating concentrations of lipoprotein-borne lipids including cholesterol and triglycerides.

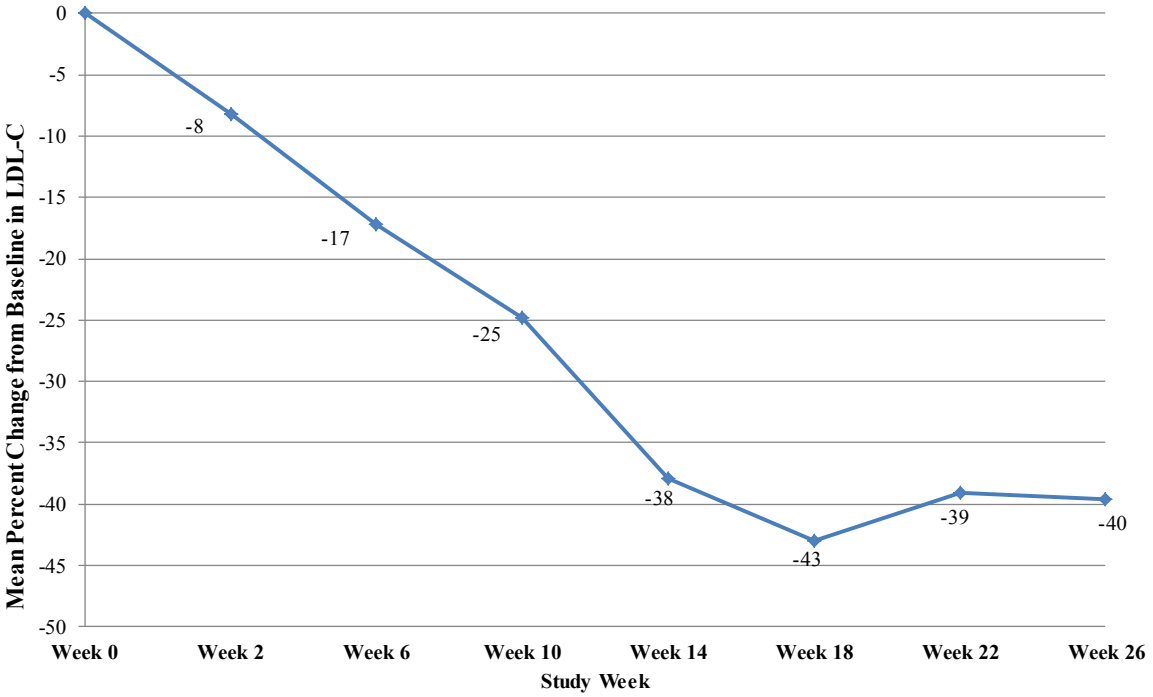
Clinical efficacy and safety

A single arm, open-label study (UP1002/AEGR-733-005) evaluated the efficacy and safety of lomitapide when co-administered with a low-fat diet and other lipid-lowering therapies in adult

patients with HoFH. Patients were instructed to maintain a low-fat diet (<20% calories from fat) and their lipid-lowering therapies at study entry, including apheresis if applicable, from 6 weeks prior to baseline through at least Week 26. The dose of lomitapide was escalated from 5 mg to an individually determined maximum tolerated dose up to 60 mg. After Week 26, patients remained on lomitapide to determine the effects of longer-term treatment and were allowed to change background lipid-lowering therapies. The study provided for a total of 78 weeks of treatment.

Twenty-nine patients were enrolled, of whom 23 completed through Week 78. Sixteen males (55%) and 13 females (45%) were included with a mean age of 30.7 years, ranging from 18 to 55 years. The mean dose of lomitapide was 45 mg at Week 26 and 40 mg at Week 78. At Week 26, the mean percent change in LDL-C from baseline of LDL-C was -40% ($p<0.001$) in the Intent to Treat (ITT) population. Mean percent change from baseline through Week 26 using last observation carried forward (LOCF) to each assessment is shown in Figure 1.

**Figure 1: Mean percent changes from baseline in LDL-C in the major effectiveness study UP1002/AEGR-733-005 through Week 26 (the Primary Endpoint) using LOCF to each assessment (N=29)**




Changes in lipids and lipoproteins through Week 26 and Week 78 of lomitapide treatment are presented in Table 5.

**Table 5: Absolute values and percent changes from baseline to Weeks 26 and 78 in lipids and lipoproteins (major effectiveness study UP1002/AEGR-733-005)**

| Parameter (units) | Baseline | Week 26/LOCF (N=29) | | | Week 78 (N=23) | | |
|---|---|---|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | % Change | p-value[b] | Mean (SD) | % Change | p-value[b] |
| LDL-C, direct (mg/dL) | 336 (114) | 190 (104) | -40 | <0.001 | 210 (132) | -38 | <0.001 |
| Total Cholesterol (TC) (mg/dL) | 430 (135) | 258 (118) | -36 | <0.001 | 281 (149) | -35 | <0.001 |
| Apolipoprotein B (apo B) (mg/dL) | 259 (80) | 148 (74) | -39 | <0.001 | 151 (89) | -43 | <0.001 |
| Triglycerides (TG) (mg/dL)[a] | 92 | 57 | -45 | 0.009 | 59 | -42 | 0.012 |
| Non high-density lipoprotein cholesterol (Non-HDL-C) (mg/dL) | 386 (132) | 217 (113) | -40 | <0.001 | 239 (146) | -39 | <0.001 |
| Very-low-density lipoprotein cholesterol (VLDL-C) (mg/dL) | 21 (10) | 13 (9) | -29 | 0.012 | 16 (15) | -31 | 0.013 |
| Lipoprotein (a) (Lp(a)) (nmol/L)[a] | 66 | 61 | -13 | 0.094 | 72 | -4 | <0.842 |
| High-density lipoprotein cholesterol (HDL-C) (mg/dL) | 44 (11) | 41 (13) | -7 | 0.072 | 43 (12) | -4.6 | 0.246 |

[a] Median presented for TG and Lp(a). p-value is based on the mean percent change
[b] p-value on the mean percent change from baseline based on paired t-test

At both Week 26 and Week 78, there were significant reductions in LDL-C, TC, apo B, TG, non-HDL-C, VLDL-C and changes in HDL-C trended lower at Week 26 and returned to baseline levels by Week 78.

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

At baseline, 93% were on a statin, 76% were on ezetimibe, 10% on niacin, 3% on a bile acid sequestrant and 62% were receiving apheresis. Fifteen of 23 (65%) patients had their lipid-lowering treatment reduced by Week 78, including planned and unplanned reductions/interruptions. Apheresis was discontinued in 3 out of 13 patients who were on it at Week 26, and frequency was reduced in 3 patients while maintaining low LDL-C levels through Week 78. The clinical benefit of reductions in background lipid-lowering therapy, including apheresis, is not certain.

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 and 1 having LDL-C <70 mg/dL at that time point.

In this study, 10 patients experienced elevations in AST and/or ALT >3 x ULN (see Table 6).

**Table 6: Highest liver function test results post first dose (major effectiveness study UP1002/AEGR-733-005)**

| Parameter/Abnormality | N (%) |
|---|---|
| ALT | |
| Number of Patients with Assessments | 29 |
| >3 to ≤5 x ULN | 6 (20.7) |
| >5 to ≤10 x ULN | 3 (10.3) |
| >10 to ≤20 x ULN | 1 (3.4) |
| >20 x ULN | 0 |
| AST | |
| Number of Patients with Assessments | 29 |
| >3 to ≤5 x ULN | 5 (17.2) |
| >5 to ≤10 x ULN | 1 (3.4) |
| >10 to ≤20 x ULN | 0 |
| >20 x ULN | 0 |

Elevations in ALT and/or AST >5 x ULN were managed with a dose reduction or temporary suspension of lomitapide dosing, and all patients were able to continue with study drug treatment. No clinically meaningful elevations in total bilirubin or alkaline phosphatase were observed. Hepatic fat was prospectively measured using MRS in all eligible patients during the clinical trial (Table 7). Data from individuals who had repeat measurements after stopping lomitapide show that hepatic fat accumulation is reversible, but whether histological sequelae remain is unknown.

**Table 7: Maximum categorical changes in % hepatic fat (major effectiveness study UP1002/AEGR-733-005)**

| 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) |

The European Medicines Agency has deferred the obligation to submit the results of studies with Lojuxta in one or more subsets of the paediatric population in HoFH (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption

The absolute oral bioavailability of lomitapide is 7%. Absorption is not limited by penetration of the drug across the intestinal barrier but is predominantly influenced by an extensive first pass effect. Peak plasma concentrations of lomitapide were reached 4-8 hours following oral dosing. Lomitapide pharmacokinetics is approximately dose-proportional for oral single doses in the therapeutic range. Doses higher than 60 mg suggest a trend toward nonlinearity and are not recommended.

Upon multiple dosing $C_{max}$ and AUC increased in approximate proportion to lomitapide dose. $C_{max}$ and AUC were increased following either a high-fat meal (77% and 58%, respectively) or low fat meal (70% and 28%, respectively). Accumulation of lomitapide in plasma was consistent with that predicted after a single dose following once daily oral dosing above 25 mg for up to 4 weeks. Inter-individual variability in lomitapide AUC was approximately 50%.

At steady state the accumulation of lomitapide was 2.7 at 25 mg and 3.9 at 50 mg.

Distribution

Following intravenous administration, the volume of distribution of lomitapide was high (mean=1200 litres) despite a high degree (>99.8%) of binding to plasma protein. In animal studies lomitapide was highly concentrated (200-fold) in the liver.

Biotransformation

Lomitapide is extensively metabolised, predominantly by CYP3A4. CYP isoforms 2E1, 1A2, 2B6, 2C8, and 2C19 are involved to a lesser extent and isoforms 2D6 and 2C9 are not involved in the metabolism of lomitapide.

Elimination

Following administration of a radiolabeled oral solution dose to healthy subjects, 93% of the administered dose was recovered in urine and faeces. Approximately 33% of the radioactivity was excreted in urine as metabolites. The remainder was excreted in faeces, primarily as oxidised metabolites. The elimination half-life of lomitapide was approximately 29 hours.

Special populations

Data in the pivotal clinical trial were analyzed with respect to the impact of potential covariates on lomitapide exposure. Of the parameters examined (race, body mass index (BMI), gender, weight, age), only BMI could be classified as a potential covariate.

*Age and gender*

There was no clinically relevant effect of age (18-64 years) or gender on the pharmacokinetics of lomitapide.

*Race*

No dose adjustment is required for Caucasian or Latino patients. There is insufficient information to determine if Lojuxta requires dose adjustment in other races. However, since the medicinal product is dosed in an escalating fashion according to individual patient safety and tolerability, no adjustment to the dosing regimen is recommended based on race.

*Renal insufficiency*

In the renal impairment population, lomitapide was only studied in patients with end-stage renal disease (ESRD). A pharmacokinetic study in patients with ESRD undergoing hemodialysis demonstrated a 36% increase in mean lomitapide plasma concentration compared to matched healthy controls. The terminal half-life of lomitapide was not affected.

*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. Lojuxta has not been studied in patients with severe hepatic impairment (Child-Pugh score 10-15).

*Paediatric population*

Lojuxta has not been investigated in children less than 18 years of age.

*Elderly population*

Lojuxta has not been investigated in patients aged 65 years or older.

## 5.3 Preclinical safety data

In repeat-dose oral toxicology studies in rodents and dogs, the principal drug-related findings were lipid accumulation in the small intestine and/or liver associated with decreases in serum cholesterol and/or triglyceride levels. These changes are secondary to the mechanism of action of lomitapide. Other liver-related changes in repeat-dose toxicity studies in rats and dogs included increased serum aminotransferases, subacute inflammation (rats only), and single-cell necrosis. In a 1 year repeat-dose study in dogs there were no microscopic changes in the liver although serum AST was minimally increased in females.

Pulmonary histiocytosis was observed in rodents. Decreased red blood cell parameters as well as poikilocytosis and/or anisocytosis were observed in dogs. Testicular toxicity was observed in dogs at 205 times the human exposure (AUC) at 60 mg in a 6-month study. No adverse effects on the testes were observed in a 1-year study in dogs at 64 times the human exposure at 60 mg.

In a dietary carcinogenicity study in mice, lomitapide was administered up to 104 weeks at doses ranging from 0.3 to 45 mg/kg/day. There were statistically significant increases in the incidences of liver adenoma and carcinoma at doses ≥1.5 mg/kg/day in males (≥ 2 times the human exposure at 60 mg daily based on AUC) and ≥7.5 mg/kg/day in females (≥ 9 times the human exposure at 60 mg based on AUC). Incidences of small intestinal carcinoma and/or combined adenoma and carcinoma (rare tumours in mice) were significantly increased at doses ≥15 mg/kg/day in males (≥ 26 times the human exposure at 60 mg based on AUC) and at 15 mg/kg/day in females (22 times the human exposure at 60 mg based on AUC).

In an oral carcinogenicity study in rats, lomitapide was administered up to 99 weeks at doses up to 7.5 mg/kg/day in males and 2.0 mg/kg/day in females. Focal hepatic fibrosis was observed in males and females and hepatic cystic degeneration was observed in males only. In high-dose males, an increased incidence of pancreatic acinar cell adenoma was observed at an exposure 6 times that in humans at 60 mg based on AUC.

Lomitapide was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* studies.

Lomitapide had no effect on reproductive function in female rats at doses up to 1 mg/kg or in male rats at doses up to 5 mg/kg. Systemic exposures to lomitapide at these doses were estimated to be 4 times (females) and 5 times (males) higher than the human exposure at 60 mg based on AUC.

Lomitapide was teratogenic in rats in the absence of maternal toxicity at an exposure (AUC) estimated to be twice that in humans at 60 mg. There was no evidence of embryofoetal toxicity in rabbits at 3 times the maximum recommended human dose (MRHD) of 60 mg based on body surface area. Embryofoetal toxicity was observed in rabbits in the absence of maternal toxicity at ≥6.5 times the MRHD. In ferrets, lomitapide was both maternally toxic and teratogenic at <1 times the MRHD.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule content
Pregelatinised starch (maize)
Sodium starch glycolate
Microcrystalline cellulose
Lactose monohydrate
Silica, colloidal anhydrous
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)

Printing ink
Shellac
Black iron oxide (E172)
Propylene glycol

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years.

### 6.4 Special precautions for storage

Store below 30°C.
Keep the bottle tightly closed in order to protect from moisture.

### 6.5 Nature and contents of container

High density polyethylene (HDPE) bottle fitted with a polyester/aluminium foil/cardboard induction seal and polypropylene screw cap.

Package sizes are:
28 capsules

### 6.6 Special precautions for disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Aegerion Pharmaceuticals Ltd
Lakeside House
1 Furzeground Way
Stockley Park East
Uxbridge UB11 1BD
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/851/003

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 July 2013

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Lojuxta 30 mg hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains lomitapide mesylate equivalent to 30 mg lomitapide.

Excipient with known effect
Each hard capsule contains 194.84 mg of lactose (as monohydrate) (see section 4.4).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Capsule, hard.

The capsule is an orange cap/yellow body hard capsule of 21.6 mm, printed with black ink imprinted with “30 mg” on body and “A733” on cap.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Lojuxta is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH).

Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism) must be excluded.

### 4.2 Posology and method of administration

Treatment with Lojuxta should be initiated and monitored by a physician experienced in the treatment of lipid disorders.

Posology

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 to the maximum recommended dose of 60 mg (see section 4.8).

The dose should be escalated gradually to minimise the incidence and severity of gastrointestinal side effects and aminotransferase elevations.

Administration with food may increase exposure to Lojuxta. Lojuxta should be taken on an empty stomach, at least 2 hours after the evening meal because the fat content of a recent meal may adversely impact gastrointestinal tolerability.

The occurrence and severity of gastrointestinal adverse reactions associated with the use of Lojuxta decreases in the presence of a low fat diet. Patients should follow a diet supplying less than 20% of energy from fat prior to initiating Lojuxta treatment, and should continue this diet during treatment. Dietary counselling should be provided.

Patients should avoid consumption of grapefruit juice (see sections 4.4 and 4.5).

For patients on a stable maintenance dose of Lojuxta who receive atorvastatin either:

- Separate the dose of the medications by 12 hours

OR

- Decrease the dose of Lojuxta by half.

Patients on 5 mg should remain on 5 mg.
Careful titration may then be considered according to LDL-C response and safety/tolerability.
Upon discontinuation of atorvastatin the dose of Lojuxta should be up-titrated according to LDL-C response and safety/tolerability.

For patients on a stable maintenance dose of Lojuxta who receive any other weak CYP3A4 inhibitor, separate the dose of the medications (Lojuxta and the weak CYP3A4 inhibitor) by 12 hours.

Consider limiting the maximum dose of Lojuxta according to desired LDL-C response.
Exercise additional caution if administering more than 1 weak CYP3A4 inhibitor with Lojuxta.

Based on observations of decreased essential fatty acid and vitamin E levels in clinical trials, patients should take daily dietary supplements that provide 400 IU vitamin E and approximately 200 mg linoleic acid, 110 mg eicosapentaenoic acid (EPA), 210 mg alpha linolenic acid (ALA) and 80 mg docosahexaenoic acid (DHA) per day, throughout treatment with Lojuxta.

*Elderly population*

There is limited experience with Lojuxta in patients aged 65 years or older. Therefore, particular caution should be exercised in these patients.

Since the recommended dose regimen involves starting at the low end of the dosing range and escalating cautiously according to individual patient tolerability, no adjustment to the dosing regimen is recommended for the elderly.

*Hepatic impairment*

Lojuxta is contraindicated in patients with moderate or severe hepatic impairment including patients with unexplained persistent abnormal liver function tests (see section 5.2).

Patients with mild hepatic impairment (Child-Pugh A) should not exceed 40 mg daily.

*Renal impairment*

Patients with end-stage renal disease receiving dialysis should not exceed 40 mg daily (see section 5.2).

*Paediatric population*

The safety and efficacy of Lojuxta in children <18 years have not been established and the use of this medicinal product in children is therefore not recommended. No data are available.

Method of administration

Oral use.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests.
- Patients with a known significant or chronic bowel disease such as inflammatory bowel disease or malabsorption.
- Concomitant administration of >40 mg simvastatin (see section 4.5).
- Concomitant use of Lojuxta with strong or moderate cytochrome P450 (CYP) 3A4 inhibitors (e.g., antifungal azoles such as itraconazole, fluconazole,ketoconazole, voriconazole, posaconazole; macrolide antibiotics such as erythromycin or clarithromycin; ketolide antibiotics such as telithromycin; HIV protease inhibitors; the calcium channel blockers diltiazem and verapamil, and the anti-arrhythmic dronedarone [see section 4.5]).
- Pregnancy (see section 4.6).

## 4.4 Special warnings and precautions for use

Liver enzyme abnormalities and liver monitoring

Lomitapide can cause elevations in alanine aminotransferase [ALT] and aspartate aminotransferase [AST] and hepatic steatosis. The extent to which lomitapide-associated hepatic steatosis promotes the elevations in aminotransferase is unknown. Although cases of hepatic dysfunction (elevated aminotransferase with increase in bilirubin or International Normalized Ratio [INR]) or hepatic failure have not been reported, there is concern that lomitapide could induce steatohepatitis, which can progress to cirrhosis over several years. The clinical studies supporting the safety and efficacy of lomitapide in HoFH would have been unlikely to detect this adverse outcome given their size and duration.

Elevations in aminotransferases (ALT and/or AST) are associated with lomitapide (see section 5.1). There were no concomitant or subsequent clinically meaningful elevations in serum bilirubin, INR, or alkaline phosphatase. Liver enzyme changes occur most often during dose escalation, but may occur at any time during therapy.

Monitoring of liver function tests

Measure ALT, AST, alkaline phosphatase, total bilirubin, gamma-glutamyl transferase (gamma-GT) and serum albumin before initiation of treatment with Lojuxta. The medicinal product is contraindicated in patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests. If the baseline liver-related tests are abnormal, consider initiating the medicinal product after appropriate investigation by a hepatologist and the baseline abnormalities are explained or resolved.

During the first year, measure liver-related tests (ALT and AST, at a minimum) prior to each increase in dose or monthly, whichever occurs first. After the first year, do these tests at least every 3 months and before any increase in dose. Decrease the dose of Lojuxta if elevations of aminotransferase are observed and discontinue treatment for persistent or clinically significant elevations (see Table 1 for specific recommendations).

Dose modification based on elevated hepatic aminotransferases

Table 1 summarizes recommendations for dose adjustment and monitoring for patients who develop elevated aminotransferase during therapy with Lojuxta.

**Table 1: Dose Adjustment and Monitoring for Patients with Elevated Aminotransferases**

| ALT or AST | Treatment and monitoring recommendations* |
|---|---|
| ≥3x and <5x Upper Limit of Normal (ULN) | • Confirm elevation with a repeat measurement within one week.<br>• If confirmed, reduce the dose and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR).<br>• Repeat tests weekly and withhold dosing if there are signs of abnormal liver function (increase in bilirubin or INR), if aminotransferase levels rise above 5x ULN, or if aminotransferase levels do not fall below 3x ULN within approximately 4 weeks. Refer patients with persistent elevations in aminotransferase >3x ULN to a hepatologist for further investigation.<br>• If resuming Lojuxta after aminotransferase levels resolve to <3x ULN, consider reducing the dose and monitor liver-related tests more frequently. |
| ≥5x ULN | • Withhold dosing and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR). If aminotransferase levels do not fall below 3x ULN within approximately 4 weeks refer the patient to a hepatologist for further investigation.<br>• If resuming Lojuxta after aminotransferase levels 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 aminotransferase 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 Lojuxta and refer the patient to a hepatologist for further investigation.

Reintroduction of treatment may be considered if the benefits are considered to outweigh the risks associated with potential liver disease.

Hepatic steatosis and risk of progressive liver disease

Consistent with the mechanism of action of lomitapide, most treated patients exhibited increases in hepatic fat content. In an open-label Phase 3 study, 18 of 23 patients with HoFH developed hepatic steatosis (hepatic fat >5.56%) as measured by nuclear magnetic resonance spectroscopy (MRS) (see section 5.1). The median absolute increase in hepatic fat was 6% after both 26 weeks and 78 weeks of treatment, from 1% at baseline, measured by MRS. Hepatic steatosis is a risk factor for progressive liver disease including steatohepatitis and cirrhosis. The long term consequences of hepatic steatosis associated with Lojuxta treatment are unknown. Clinical data suggest that hepatic fat accumulation is reversible after stopping treatment with Lojuxta, but whether histological sequelae remain is unknown, especially after long-term use.

Monitoring for evidence of progressive liver disease.

Regular screening for steatohepatitis/fibrosis should be performed at baseline and on an annual basis using the following imaging and biomarker evaluations:

- Imaging for tissue elasticity, e.g. Fibroscan, acoustic radiation force impulse (ARFI), or magnetic resonance (MR) elastography

- Gamma-GT and serum albumin to detect possible liver injury

- At least one marker from each of the following categories:

    - High sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), CK-18 Fragment, NashTest (liver inflammation)
    - Enhanced Liver Fibrosis (ELF) panel, Fibrometer, AST/ALT ratio, Fib-4 score, Fibrotest (liver fibrosis)

The performance of these tests and their interpretation should involve collaboration between the treating physician and the hepatologist. Patients with results suggesting the presence of steatohepatitis or fibrosis should be considered for liver biopsy.

If a patient has biopsy-proven steatohepatitis or fibrosis, the benefit-risk should be reassessed and treatment stopped if necessary.

Dehydration

Post-marketing reports of dehydration and hospitalisation in patients treated with lomitapide have been reported. Patients treated with lomitapide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Concomitant use of CYP3A4 inhibitors

Lomitapide appears to be a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with Lojuxta is contraindicated (see section 4.3). In the lomitapide clinical trials, one patient with HoFH developed markedly elevated aminotransferase (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, Lojuxta should be stopped during the course of treatment.

Weak CYP3A4 inhibitors are expected to increase the exposure of lomitapide when taken simultaneously. When administered with atorvastatin, the dose of Lojuxta should either be taken 12 hours apart or be decreased by half (see section 4.2). The dose of Lojuxta should be administered 12 hours apart from any other weak CYP3A4 inhibitor.

Concomitant use of CYP3A4 inducers

Medicines that induce CYP3A4 would be expected to increase the rate and extent of metabolism of lomitapide. CYP3A4 inducers exert their effect in a time-dependent manner, and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2 weeks to decline.

Co-administration of a CYP3A4 inducer is expected to reduce the effect of Lojuxta. Any impact on efficacy is likely to be variable. When co-administering CYP3A4 inducers (i.e. aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, glucocorticoids, modafinil and phenytoin) with Lojuxta, the possibility of a drug-drug interaction affecting efficacy should be considered. The use of St. John's Wort should be avoided with Lojuxta.

It is recommended to increase the frequency of LDL-C assessment during such concomitant use and consider increasing the dose of Lojuxta to ensure maintenance of the desired level of efficacy if the CYP3A4 inducer is intended for chronic use. On withdrawal of a CYP3A4 inducer, the possibility of increased exposure should be considered and a reduction in the dose of Lojuxta may be necessary.

Concomitant use of HMG-CoA reductase inhibitors ('statins')

Lomitapide increases plasma concentrations of statins. Patients receiving Lojuxta as adjunctive therapy to a statin should be monitored for adverse events that are associated with the use of high doses of statins. Statins occasionally cause myopathy. In rare cases, myopathy may take the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and can lead to fatality. All patients receiving Lojuxta in addition to a statin should be advised of the potential increased risk of myopathy and told to report promptly any unexplained muscle pain, tenderness, or weakness. Doses of simvastatin >40 mg should not be used with Lojuxta (see section 4.3).

Grapefruit juice

Grapefruit juice must be omitted from the diet while patients are treated with Lojuxta.

Risk of supratherapeutic or subtherapeutic anticoagulation with coumarin based anticoagulants

Lomitapide increases the plasma concentrations of warfarin. Increases in the dose of Lojuxta may lead to supratherapeutic anticoagulation, and decreases in the dose may lead to subtherapeutic anticoagulation. Difficulty controlling INR contributed to early discontinuation from the Phase 3 trial for one of five patients taking concomitant warfarin. Patients taking warfarin should undergo regular monitoring of the INR, especially after any changes in Lojuxta dosage. The dose of warfarin should be adjusted as clinically indicated.

Use of alcohol

Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. In the Phase 3 trial, 3 of 4 patients with ALT elevations >5x ULN reported alcohol consumption beyond the limits recommended in the protocol. The use of alcohol during Lojuxta treatment is not recommended.

Hepatotoxic agents

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

Reduced absorption of fat-soluble vitamins and serum fatty acids

Given its mechanism of action in the small intestine, lomitapide may reduce the absorption of fat-soluble nutrients. In the Phase 3 trial, patients were provided daily dietary supplements of vitamin E, linoleic acid, ALA, EPA and 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 lomitapide treatment of up to 78 weeks. Patients treated with Lojuxta should take daily supplements that contain 400 international units vitamin E and approximately 200 mg linoleic acid, 210 mg ALA, 110 mg EPA, and 80 mg DHA.

Contraception measures in women of child-bearing potential

Before initiating treatment in women of child-bearing potential, appropriate advice on effective methods of contraception should be provided, and effective contraception initiated. Patients taking oestrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting (see section 4.5). Oestrogen-containing oral contraceptives are weak CYP3A4 inhibitors (see section 4.2).

Patients should be advised to immediately contact their physician and stop taking Lojuxta if they become pregnant (see section 4.6).

Lactose

Lojuxta contains lactose and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption.

## 4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on Lojuxta and other forms of interaction

**Table 2: Interactions between Lojuxta and other medicinal products and other forms of interaction**

| Medicinal products | Effects on lomitapide levels | Recommendation concerning co-administration with Lojuxta |
|---|---|---|
| Inhibitors of CYP3A4 | When lomitapide 60 mg was co-administered with ketoconazole 200 mg twice daily, a strong inhibitor of CYP3A4, lomitapide AUC increased approximately 27-fold and $C_{max}$ increased approximately 15-fold.<br><br>Interactions between moderate CYP3A4 inhibitors and lomitapide have not been studied.<br><br>Moderate CYP3A4 inhibitors are predicted to have a substantial impact on lomitapide's pharmacokinetics. Concomitant use of moderate CYP3A4 inhibitors are expected to increase lomitapide exposure by 4-10 fold based on the results of the study with the strong CYP3A4 inhibitor ketoconazole and on historical data for the model CYP3A4 probe midazolam.<br><br>Weak CYP3A4 inhibitors are expected to increase the exposure of lomitapide when taken simultaneously.<br><br>When lomitapide 20 mg was co-administered simultaneously with atorvastatin, a weak CYP3A4 inhibitor, lomitapide AUC and $C_{max}$ increased approximately 2-fold. When the dose of lomitapide was taken 12 hours apart from atorvastatin, | Use of strong or moderate inhibitors of CYP3A4 is contraindicated with Lojuxta. If treatment with antifungal azoles (e.g., itraconazole, ketoconazole, fluconazole, voriconazole, posaconazole); the antiarrhythmic dronedarone; macrolide antibiotics (e.g., erythromycin, clarithromycin); ketolide antibiotics (e.g., telithromycin); HIV protease inhibitors; the calcium channel blockers diltiazem and verapamil is unavoidable, therapy with Lojuxta should be suspended during the course of treatment (see sections 4.3 and 4.4).<br><br>Grapefruit juice is a moderate inhibitor of CYP3A4 and is expected to substantially increase exposure to lomitapide. Patients taking Lojuxta should avoid consumption of grapefruit juice.<br><br>When administered with atorvastatin, the dose of Lojuxta should either be taken 12 hours apart or be decreased by half (see section 4.2). The dose of Lojuxta should be taken 12 hours apart from any other concomitant weak CYP3A4 inhibitors. Examples of weak CYP3A4 inhibitors include: alprazolam, amiodarone, amlodipine, atorvastatin, azithromycin, bicalutamide, cilostazol, cimetidine, ciclosporin, clotrimazole, fluoxetine, fluvoxamine, fosaprepitant, ginkgo, goldenseal, isoniazid, ivacaftor, lacidipine, lapatinib, linagliptin, nilotinib, oestrogen-containing oral contraceptives, pazopanib, peppermint oil, propiverine, ranitidine, ranolazine, roxithromycin, Seville oranges, tacrolimus, ticagrelor and tolvaptan. This |

| Medicinal products | Effects on lomitapide levels | Recommendation concerning co-administration with Lojuxta |
|---|---|---|
| | no clinically meaningful increase in lomitapide exposure was observed.<br><br>When lomitapide 20 mg was co-administered simultaneously or 12 hours apart with ethinyl estradiol/norgestimate, a weak CYP3A4 inhibitor, no clinically meaningful increase in lomitapide exposure was observed. | list is not intended to be comprehensive and prescribers should check the prescribing information of drugs to be co-administered with Lojuxta for potential CYP3A4 mediated interactions.<br><br>The effect of administration of more than one weak CYP3A4 inhibitor has not been tested, but the effect on the exposure of lomitapide is expected to be greater than for co-administration of the individual inhibitors with lomitapide.<br><br>Exercise additional caution if administering more than 1 weak CYP3A4 inhibitor with Lojuxta. |
| Inducers of CYP3A4 | Medicines that induce CYP3A4 would be expected to increase the rate and extent of metabolism of lomitapide. Consequently, this would reduce the effect of lomitapide. Any impact on efficacy is likely to be variable. | When co-administering CYP3A4 inducers (i.e., aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, St John's Wort, glucocorticoids, modafinil and phenytoin) with Lojuxta, the possibility of a drug-drug interaction affecting efficacy should be considered. It is recommended to increase the frequency of LDL-C assessment during such concomitant use and consider increasing the dose of Lojuxta to ensure maintenance of the desired level of efficacy if the CYP3A4 inducer is intended for chronic use. |
| Bile acid sequestrants | Lomitapide has not been tested for interaction with bile acid sequestrants (resins such as colesevelam and cholestyramine). | Because bile acid sequestrants can interfere with the absorption of oral medicines, bile acid sequestrants should be taken at least 4 hours before or at least 4 hours after Lojuxta. |

Effects of lomitapide on other medicinal products

*HMG-CoA Reductase Inhibitors ("Statins"):* Lomitapide increases plasma concentrations of statins. When lomitapide 60 mg was administered to steady state prior to simvastatin 40 mg, simvastatin acid AUC and $C_{max}$ increased 68% and 57%, respectively. When lomitapide 60 mg was administered to steady state prior to atorvastatin 20 mg, atorvastatin acid AUC and $C_{max}$ increased 52% and 63%, respectively. When lomitapide 60 mg was administered to steady state prior to rosuvastatin 20 mg, rosuvastatin $T_{max}$ increased from 1 to 4 hours, AUC was increased 32%, and its $C_{max}$ was unchanged. The risk of myopathy with simvastatin is dose related. Use of Lojuxta is contraindicated in patients treated with high doses of simvastatin (>40 mg) (see sections 4.3 and 4.4).

*Coumarin anticoagulants:* When lomitapide 60 mg was administered to steady state and 6 days following warfarin 10 mg, INR increased 1.26-fold. AUCs for R(+)-warfarin and S(-)-warfarin increased 25% and 30%, respectively. $C_{max}$ for R(+)-warfarin and S(-)-warfarin increased 14% and 15%, respectively. In patients taking coumarins (such as warfarin) and Lojuxta concomitantly, INR

should be determined before starting Lojuxta and monitored regularly with dosage of coumarins adjusted as clinically indicated (see section 4.4).

*Fenofibrate, niacin and ezetimibe*: When lomitapide was administered to steady state prior to micronised fenofibrate 145 mg, extended release niacin 1000 mg, or ezetimibe 10 mg, no clinically significant effects on the exposure of any of these medicinal products were observed. No dose adjustments are required when co-administered with Lojuxta.

*Oral contraceptives:* When lomitapide 50 mg was administered to steady state along with an oestrogen-based oral contraceptive, no clinically meaningful or statistically significant impact on the pharmacokinetics of the components of the oral contraceptive (ethinyl estradiol and 17-deacetyl norgestimate, the metabolite of norgestimate) was observed. Lomitapide is not expected to directly influence the efficacy of oestrogen based oral contraceptives; however diarrhoea and/or vomiting may reduce hormone absorption. In cases of protracted or severe diarrhoea and/or vomiting lasting more than 2 days, additional contraceptive measures should be used for 7 days after resolution of symptoms.

*P-gp substrates:* Lomitapide inhibits P-gp *in vitro*, and may increase the absorption of P-gp substrates. Coadministration of Lojuxta 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 Lojuxta.

*In vitro assessment of drug interactions*: Lomitapide inhibits CYP3A4. Lomitapide does not induce CYPs 1A2, 3A4, or 2B6, and does not inhibit CYPs 1A2, 2B6, 2C9, 2C19, 2D6, or 2E1. Lomitapide is not a P-gp substrate but does inhibit P-gp. Lomitapide does not inhibit breast cancer resistance protein (BCRP).

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Lojuxta is contraindicated during pregnancy. There are no reliable data on its use in pregnant women. Animal studies have shown developmental toxicity (teratogenicity, embryotoxicity, see section 5.3). The potential risk for humans is unknown.

Use in women of child-bearing potential

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. Patients taking oestrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting. Additional contraceptive measures should be used until resolution of symptoms (see section 4.5).

Breast-feeding

It is not known whether lomitapide is excreted into human milk. Because of the potential for adverse effects based on findings in animal studies with lomitapide (see section 5.3), a decision should be made whether to discontinue breast-feeding or discontinue the medicinal product, taking into account the importance of the medicinal product to the mother.

Fertility

No adverse effects on fertility were observed in male and female rats administered lomitapide at systemic exposures (AUC) estimated to be 4 to 5 times higher than in humans at the maximum recommended human dose (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Lojuxta may have a minor influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile

The most serious adverse reactions during treatment were liver aminotransferase abnormalities (see section 4.4).

The most common adverse reactions were gastrointestinal effects. Gastrointestinal adverse reactions were reported by 27 (93%) of 29 patients in the Phase 3 clinical trial. Diarrhoea 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. Gastrointestinal adverse reactions occurred more frequently during the dose escalation phase of the study and decreased once patients established the maximum tolerated dose of lomitapide.

Gastrointestinal adverse reactions of severe intensity were reported by 6 (21%) of 29 patients in the Phase 3 clinical trial, with the most common being diarrhoea (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.

The most commonly reported adverse reactions of severe intensity were diarrhoea (4 subjects, 14%), vomiting (3 patients, 10%), and abdominal distension and ALT increased (2 subjects each, 7%).

Tabulated list of adverse reactions

Frequency of the adverse reactions is defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 3 lists all adverse reactions reported across the 35 patients treated in the Phase 2 Study UP1001 and in the Phase 3 Study UP1002/AEGR-733-005 or its extension study AEGR-733-012.

**Table 3: Frequency of Adverse Reactions in HoFH Patients**

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| Infections and infestations | Common | Gastroenteritis |
| Metabolism and nutrition disorders | Very common | Decreased appetite |
| | Not known | Dehydration |
| Nervous system disorders | Common | Dizziness<br>Headache<br>Migraine |
| Gastrointestinal disorders | Very common | Diarrhoea<br>Nausea<br>Vomiting<br>Abdominal discomfort<br>Dyspepsia<br>Abdominal pain<br>Abdominal pain upper<br>Flatulence<br>Abdominal distension<br>Constipation |
| | Common | Gastritis<br>Rectal tenesmus<br>Aerophagia<br>Defaecation urgency<br>Eructation<br>Frequent bowel movements<br>Gastric dilatation<br>Gastric disorder<br>Gastrooesophageal reflux disease<br>Haemorrhoidal haemorrhage<br>Regurgitation |
| Hepatobiliary disorders | Common | Hepatic steatosis<br>Hepatotoxicity<br>Hepatomegaly |
| Skin and subcutaneous tissue disorders | Common | Ecchymosis<br>Papule<br>Rash erythematous<br>Xanthoma |
| | Not known | Alopecia |
| Musculoskeletal and connective tissue disorders | Not known | Myalgia |
| General disorders and administration site conditions | Common | Fatigue |
| Investigations | Very common | Alanine aminotransferase increased<br>Aspartate aminotransferase increased<br>Weight decreased |
| | Common | International normalised ratio increased<br>Blood alkaline phosphatase increased<br>Blood potassium decreased<br>Carotene decreased<br>International normalised ratio abnormal<br>Liver function test abnormal<br>Prothrombin time prolonged<br>Transaminases increased<br>Vitamin E decreased<br>Vitamin K decreased |

Table 4 lists all adverse reactions for subjects who received lomitapide monotherapy (N=291) treated in Phase 2 studies in subjects with elevated LDL-C (N=462).

**Table 4: Frequency of Adverse Reactions in Elevated LDL-C Patients**

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| Infections and infestations | Uncommon | Gastroenteritis<br>Gastrointestinal infection<br>Influenza<br>Nasopharyngitis<br>Sinusitis |
| Blood and lymphatic system disorders | Uncommon | Anaemia |
| Metabolism and nutrition disorders | Common | Decreased appetite |
| | Uncommon | Dehydration<br>Increased appetite |
| Nervous system disorders | Uncommon | Paraesthesia<br>Somnolence |
| Eye disorders | Uncommon | Eye swelling |
| Ear and labyrinth disorders | Uncommon | Vertigo |
| Respiratory, thoracic and mediastinal disorders | Uncommon | Pharyngeal lesion<br>Upper-airway cough syndrome |
| Gastrointestinal disorders | Very common | Diarrhoea<br>Nausea<br>Flatulence |
| | Common | Abdominal pain upper<br>Abdominal distension<br>Abdominal pain<br>Vomiting<br>Abdominal discomfort<br>Dyspepsia<br>Eructation<br>Abdominal pain lower<br>Frequent bowel movements |
| | Uncommon | Dry mouth<br>Faeces hard<br>Gastrooeosophageal reflux disease<br>Abdominal tenderness<br>Epigastric discomfort<br>Gastric dilatation<br>Haematemesis<br>Lower gastrointestinal haemorrhage<br>Reflux oesophagitis |
| Hepatobiliary disorders | Uncommon | Hepatomegaly |
| Skin and subcutaneous tissue disorders | Uncommon | Blister<br>Dry skin<br>Hyperhidrosis |
| Musculoskeletal and connective tissue disorders | Common | Muscle spasms |
| | Uncommon | Arthralgia<br>Myalgia<br>Pain in extremity<br>Joint swelling<br>Muscle twitching |
| Renal and urinary disorders | Uncommon | Haematuria |

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| General disorders and administrative site conditions | Common | Fatigue<br>Asthenia |
| | Uncommon | Chest pain<br>Chills<br>Early satiety<br>Gait disturbance<br>Malaise<br>Pyrexia |
| Investigations | Common | Alanine aminotransferase increased<br>Aspartate aminotransferase increased<br>Hepatic enzyme increased<br>Liver function test abnormal<br>Neutrophil count decreased<br>White blood cell count decreased |
| | Uncommon | Weight decreased<br>Blood bilirubin increased<br>Gamma-glutamyltransferase increased<br>Neutrophil percentage increased<br>Protein urine<br>Prothrombin time prolonged<br>Pulmonary function test abnormal<br>White blood cell count increased |

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

There is no specific treatment in the event of overdose. In rodents, single oral doses of lomitapide ≥600 times higher than the maximum recommended human dose (1 mg/kg) were well tolerated. The maximum dose administered to human subjects in clinical studies was 200 mg as a single dose; there were no adverse reactions.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other lipid modifying agents, plain. ATC code: C10AX12

Mechanism of action

Lomitapide is a selective inhibitor of microsomal 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 reduces lipoprotein secretion and circulating concentrations of lipoprotein-borne lipids including cholesterol and triglycerides.

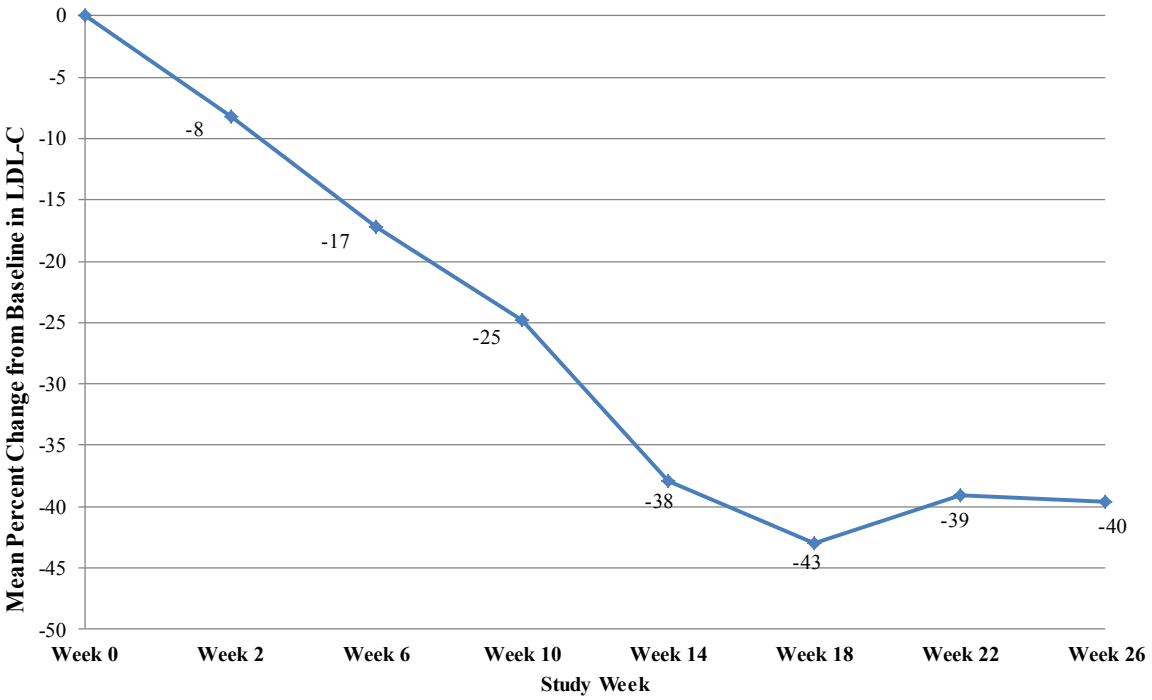
Clinical efficacy and safety

A single arm, open-label study (UP1002/AEGR-733-005) evaluated the efficacy and safety of lomitapide when co-administered with a low-fat diet and other lipid-lowering therapies in adult

patients with HoFH. Patients were instructed to maintain a low-fat diet (<20% calories from fat) and their lipid-lowering therapies at study entry, including apheresis if applicable, from 6 weeks prior to baseline through at least Week 26. The dose of lomitapide was escalated from 5 mg to an individually determined maximum tolerated dose up to 60 mg. After Week 26, patients remained on lomitapide to determine the effects of longer-term treatment and were allowed to change background lipid-lowering therapies. The study provided for a total of 78 weeks of treatment.

Twenty-nine patients were enrolled, of whom 23 completed through Week 78. Sixteen males (55%) and 13 females (45%) were included with a mean age of 30.7 years, ranging from 18 to 55 years. The mean dose of lomitapide was 45 mg at Week 26 and 40 mg at Week 78. At Week 26, the mean percent change in LDL-C from baseline of LDL-C was -40% ($p<0.001$) in the Intent to Treat (ITT) population. Mean percent change from baseline through Week 26 using last observation carried forward (LOCF) to each assessment is shown in Figure 1.

**Figure 1: Mean percent changes from baseline in LDL-C in the major effectiveness study UP1002/AEGR-733-005 through Week 26 (the Primary Endpoint) using LOCF to each assessment (N=29)**




Changes in lipids and lipoproteins through Week 26 and Week 78 of lomitapide treatment are presented in Table 5.

**Table 5: Absolute values and percent changes from baseline to Weeks 26 and 78 in lipids and lipoproteins (major effectiveness study UP1002/AEGR-733-005)**

| Parameter (units) | Baseline | Week 26/LOCF (N=29) | | | Week 78 (N=23) | | |
|---|---|---|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | % Change | p-value[b] | Mean (SD) | % Change | p-value[b] |
| LDL-C, direct (mg/dL) | 336 (114) | 190 (104) | -40 | <0.001 | 210 (132) | -38 | <0.001 |
| Total Cholesterol (TC) (mg/dL) | 430 (135) | 258 (118) | -36 | <0.001 | 281 (149) | -35 | <0.001 |
| Apolipoprotein B (apo B) (mg/dL) | 259 (80) | 148 (74) | -39 | <0.001 | 151 (89) | -43 | <0.001 |
| Triglycerides (TG) (mg/dL)[a] | 92 | 57 | -45 | 0.009 | 59 | -42 | 0.012 |
| Non high-density lipoprotein cholesterol (Non-HDL-C) (mg/dL) | 386 (132) | 217 (113) | -40 | <0.001 | 239 (146) | -39 | <0.001 |
| Very-low-density lipoprotein cholesterol (VLDL-C) (mg/dL) | 21 (10) | 13 (9) | -29 | 0.012 | 16 (15) | -31 | 0.013 |
| Lipoprotein (a) (Lp(a)) (nmol/L)[a] | 66 | 61 | -13 | 0.094 | 72 | -4 | <0.842 |
| High-density lipoprotein cholesterol (HDL-C) (mg/dL) | 44 (11) | 41 (13) | -7 | 0.072 | 43 (12) | -4.6 | 0.246 |

[a] Median presented for TG and Lp(a). p-value is based on the mean percent change
[b] p-value on the mean percent change from baseline based on paired t-test

At both Week 26 and Week 78, there were significant reductions in LDL-C, TC, apo B, TG, non-HDL-C, VLDL-C and changes in HDL-C trended lower at Week 26 and returned to baseline levels by Week 78.

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

At baseline, 93% were on a statin, 76% were on ezetimibe, 10% on niacin, 3% on a bile acid sequestrant and 62% were receiving apheresis. Fifteen of 23 (65%) patients had their lipid-lowering treatment reduced by Week 78, including planned and unplanned reductions/interruptions. Apheresis was discontinued in 3 out of 13 patients who were on it at Week 26, and frequency was reduced in 3 patients while maintaining low LDL-C levels through Week 78. The clinical benefit of reductions in background lipid-lowering therapy, including apheresis, is not certain.

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 and 1 having LDL-C <70 mg/dL at that time point.

In this study, 10 patients experienced elevations in AST and/or ALT >3 x ULN (see Table 6).

**Table 6: Highest liver function test results post first dose (major effectiveness study UP1002/AEGR-733-005)**

| Parameter/Abnormality | N (%) |
|---|---|
| ALT | |
| Number of Patients with Assessments | 29 |
| >3 to ≤5 x ULN | 6 (20.7) |
| >5 to ≤10 x ULN | 3 (10.3) |
| >10 to ≤20 x ULN | 1 (3.4) |
| >20 x ULN | 0 |
| AST | |
| Number of Patients with Assessments | 29 |
| >3 to ≤5 x ULN | 5 (17.2) |
| >5 to ≤10 x ULN | 1 (3.4) |
| >10 to ≤20 x ULN | 0 |
| >20 x ULN | 0 |

Elevations in ALT and/or AST >5 x ULN were managed with a dose reduction or temporary suspension of lomitapide dosing, and all patients were able to continue with study drug treatment. No clinically meaningful elevations in total bilirubin or alkaline phosphatase were observed. Hepatic fat was prospectively measured using MRS in all eligible patients during the clinical trial (Table 7). Data from individuals who had repeat measurements after stopping lomitapide show that hepatic fat accumulation is reversible, but whether histological sequelae remain is unknown.

**Table 7: Maximum categorical changes in % hepatic fat (major effectiveness study UP1002/AEGR-733-005)**

| 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) |

The European Medicines Agency has deferred the obligation to submit the results of studies with Lojuxta in one or more subsets of the paediatric population in HoFH (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption

The absolute oral bioavailability of lomitapide is 7%. Absorption is not limited by penetration of the drug across the intestinal barrier but is predominantly influenced by an extensive first pass effect. Peak plasma concentrations of lomitapide were reached 4-8 hours following oral dosing. Lomitapide pharmacokinetics is approximately dose-proportional for oral single doses in the therapeutic range. Doses higher than 60 mg suggest a trend toward nonlinearity and are not recommended.

Upon multiple dosing $C_{max}$ and AUC increased in approximate proportion to lomitapide dose. $C_{max}$ and AUC were increased following either a high-fat meal (77% and 58%, respectively) or low fat meal (70% and 28%, respectively). Accumulation of lomitapide in plasma was consistent with that predicted after a single dose following once daily oral dosing above 25 mg for up to 4 weeks. Inter-individual variability in lomitapide AUC was approximately 50%.

At steady state the accumulation of lomitapide was 2.7 at 25 mg and 3.9 at 50 mg.

Distribution

Following intravenous administration, the volume of distribution of lomitapide was high (mean=1200 litres) despite a high degree (>99.8%) of binding to plasma protein. In animal studies lomitapide was highly concentrated (200-fold) in the liver.

Biotransformation

Lomitapide is extensively metabolised, predominantly by CYP3A4. CYP isoforms 2E1, 1A2, 2B6, 2C8, and 2C19 are involved to a lesser extent and isoforms 2D6 and 2C9 are not involved in the metabolism of lomitapide.

Elimination

Following administration of a radiolabeled oral solution dose to healthy subjects, 93% of the administered dose was recovered in urine and faeces. Approximately 33% of the radioactivity was excreted in urine as metabolites. The remainder was excreted in faeces, primarily as oxidised metabolites. The elimination half-life of lomitapide was approximately 29 hours.

Special populations

Data in the pivotal clinical trial were analyzed with respect to the impact of potential covariates on lomitapide exposure. Of the parameters examined (race, body mass index (BMI), gender, weight, age), only BMI could be classified as a potential covariate.

*Age and gender*

There was no clinically relevant effect of age (18-64 years) or gender on the pharmacokinetics of lomitapide.

*Race*

No dose adjustment is required for Caucasian or Latino patients. There is insufficient information to determine if Lojuxta requires dose adjustment in other races. However, since the medicinal product is dosed in an escalating fashion according to individual patient safety and tolerability, no adjustment to the dosing regimen is recommended based on race.

*Renal insufficiency*

In the renal impairment population, lomitapide was only studied in patients with end-stage renal disease (ESRD). A pharmacokinetic study in patients with ESRD undergoing hemodialysis demonstrated a 36% increase in mean lomitapide plasma concentration compared to matched healthy controls. The terminal half-life of lomitapide was not affected.

*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. Lojuxta has not been studied in patients with severe hepatic impairment (Child-Pugh score 10-15).

*Paediatric population*

Lojuxta has not been investigated in children less than 18 years of age.

*Elderly population*

Lojuxta has not been investigated in patients aged 65 years or older.

## 5.3 Preclinical safety data

In repeat-dose oral toxicology studies in rodents and dogs, the principal drug-related findings were lipid accumulation in the small intestine and/or liver associated with decreases in serum cholesterol and/or triglyceride levels. These changes are secondary to the mechanism of action of lomitapide. Other liver-related changes in repeat-dose toxicity studies in rats and dogs included increased serum aminotransferases, subacute inflammation (rats only), and single-cell necrosis. In a 1 year repeat-dose study in dogs there were no microscopic changes in the liver although serum AST was minimally increased in females.

Pulmonary histiocytosis was observed in rodents. Decreased red blood cell parameters as well as poikilocytosis and/or anisocytosis were observed in dogs. Testicular toxicity was observed in dogs at 205 times the human exposure (AUC) at 60 mg in a 6-month study. No adverse effects on the testes were observed in a 1-year study in dogs at 64 times the human exposure at 60 mg.

In a dietary carcinogenicity study in mice, lomitapide was administered up to 104 weeks at doses ranging from 0.3 to 45 mg/kg/day. There were statistically significant increases in the incidences of liver adenoma and carcinoma at doses ≥1.5 mg/kg/day in males (≥ 2 times the human exposure at 60 mg daily based on AUC) and ≥7.5 mg/kg/day in females (≥ 9 times the human exposure at 60 mg based on AUC). Incidences of small intestinal carcinoma and/or combined adenoma and carcinoma (rare tumours in mice) were significantly increased at doses ≥15 mg/kg/day in males (≥ 26 times the human exposure at 60 mg based on AUC) and at 15 mg/kg/day in females (22 times the human exposure at 60 mg based on AUC).

In an oral carcinogenicity study in rats, lomitapide was administered up to 99 weeks at doses up to 7.5 mg/kg/day in males and 2.0 mg/kg/day in females. Focal hepatic fibrosis was observed in males and females and hepatic cystic degeneration was observed in males only. In high-dose males, an increased incidence of pancreatic acinar cell adenoma was observed at an exposure 6 times that in humans at 60 mg based on AUC.

Lomitapide was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* studies.

Lomitapide had no effect on reproductive function in female rats at doses up to 1 mg/kg or in male rats at doses up to 5 mg/kg. Systemic exposures to lomitapide at these doses were estimated to be 4 times (females) and 5 times (males) higher than the human exposure at 60 mg based on AUC.

Lomitapide was teratogenic in rats in the absence of maternal toxicity at an exposure (AUC) estimated to be twice that in humans at 60 mg. There was no evidence of embryofoetal toxicity in rabbits at 3 times the maximum recommended human dose (MRHD) of 60 mg based on body surface area. Embryofoetal toxicity was observed in rabbits in the absence of maternal toxicity at ≥6.5 times the MRHD. In ferrets, lomitapide was both maternally toxic and teratogenic at <1 times the MRHD.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule content
Pregelatinised starch (maize)
Sodium starch glycolate
Microcrystalline cellulose
Lactose monohydrate
Silica, colloidal anhydrous
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

Printing ink
Shellac
Black iron oxide (E172)
Propylene glycol

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years.

### 6.4 Special precautions for storage

Store below 30°C.
Keep the bottle tightly closed in order to protect from moisture.

### 6.5 Nature and contents of container

High density polyethylene (HDPE) bottle fitted with a polyester/aluminium foil/cardboard induction seal and polypropylene screw cap.

Package sizes are:
28 capsules

### 6.6 Special precautions for disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Aegerion Pharmaceuticals Ltd
Lakeside House
1 Furzeground Way
Stockley Park East
Uxbridge UB11 1BD
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/851/004

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Lojuxta 40 mg hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains lomitapide mesylate equivalent to 40 mg lomitapide.

Excipient with known effect
Each hard capsule contains 259.79 mg of lactose (as monohydrate) (see section 4.4).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Capsule, hard.

The capsule is a yellow cap/white body hard capsule of 23.4 mm, printed with black ink imprinted with “40 mg” on body and “A733” on cap.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Lojuxta is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH).

Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism) must be excluded.

### 4.2 Posology and method of administration

Treatment with Lojuxta should be initiated and monitored by a physician experienced in the treatment of lipid disorders.

Posology

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 to the maximum recommended dose of 60 mg (see section 4.8).

The dose should be escalated gradually to minimise the incidence and severity of gastrointestinal side effects and aminotransferase elevations.

Administration with food may increase exposure to Lojuxta. Lojuxta should be taken on an empty stomach, at least 2 hours after the evening meal because the fat content of a recent meal may adversely impact gastrointestinal tolerability.

The occurrence and severity of gastrointestinal adverse reactions associated with the use of Lojuxta decreases in the presence of a low fat diet. Patients should follow a diet supplying less than 20% of energy from fat prior to initiating Lojuxta treatment, and should continue this diet during treatment. Dietary counselling should be provided.

Patients should avoid consumption of grapefruit juice (see sections 4.4 and 4.5).

For patients on a stable maintenance dose of Lojuxta who receive atorvastatin either:

- Separate the dose of the medications by 12 hours

OR

- Decrease the dose of Lojuxta by half.

Patients on 5 mg should remain on 5 mg.
Careful titration may then be considered according to LDL-C response and safety/tolerability.
Upon discontinuation of atorvastatin the dose of Lojuxta should be up-titrated according to LDL-C response and safety/tolerability.

For patients on a stable maintenance dose of Lojuxta who receive any other weak CYP3A4 inhibitor, separate the dose of the medications (Lojuxta and the weak CYP3A4 inhibitor) by 12 hours.

Consider limiting the maximum dose of Lojuxta according to desired LDL-C response.
Exercise additional caution if administering more than 1 weak CYP3A4 inhibitor with Lojuxta.

Based on observations of decreased essential fatty acid and vitamin E levels in clinical trials, patients should take daily dietary supplements that provide 400 IU vitamin E and approximately 200 mg linoleic acid, 110 mg eicosapentaenoic acid (EPA), 210 mg alpha linolenic acid (ALA) and 80 mg docosahexaenoic acid (DHA) per day, throughout treatment with Lojuxta.

*Elderly population*

There is limited experience with Lojuxta in patients aged 65 years or older. Therefore, particular caution should be exercised in these patients.

Since the recommended dose regimen involves starting at the low end of the dosing range and escalating cautiously according to individual patient tolerability, no adjustment to the dosing regimen is recommended for the elderly.

*Hepatic impairment*

Lojuxta is contraindicated in patients with moderate or severe hepatic impairment including patients with unexplained persistent abnormal liver function tests (see section 5.2).

Patients with mild hepatic impairment (Child-Pugh A) should not exceed 40 mg daily.

*Renal impairment*

Patients with end-stage renal disease receiving dialysis should not exceed 40 mg daily (see section 5.2).

*Paediatric population*

The safety and efficacy of Lojuxta in children <18 years have not been established and the use of this medicinal product in children is therefore not recommended. No data are available.

Method of administration

Oral use.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests.
- Patients with a known significant or chronic bowel disease such as inflammatory bowel disease or malabsorption.
- Concomitant administration of >40 mg simvastatin (see section 4.5).
- Concomitant use of Lojuxta with strong or moderate cytochrome P450 (CYP) 3A4 inhibitors (e.g., antifungal azoles such as itraconazole, fluconazole,ketoconazole, voriconazole, posaconazole; macrolide antibiotics such as erythromycin or clarithromycin; ketolide antibiotics such as telithromycin; HIV protease inhibitors; the calcium channel blockers diltiazem and verapamil, and the anti-arrhythmic dronedarone [see section 4.5]).
- Pregnancy (see section 4.6).

## 4.4 Special warnings and precautions for use

Liver enzyme abnormalities and liver monitoring

Lomitapide can cause elevations in alanine aminotransferase [ALT] and aspartate aminotransferase [AST] and hepatic steatosis. The extent to which lomitapide-associated hepatic steatosis promotes the elevations in aminotransferase is unknown. Although cases of hepatic dysfunction (elevated aminotransferase with increase in bilirubin or International Normalized Ratio [INR]) or hepatic failure have not been reported, there is concern that lomitapide could induce steatohepatitis, which can progress to cirrhosis over several years. The clinical studies supporting the safety and efficacy of lomitapide in HoFH would have been unlikely to detect this adverse outcome given their size and duration.

Elevations in aminotransferases (ALT and/or AST) are associated with lomitapide (see section 5.1). There were no concomitant or subsequent clinically meaningful elevations in serum bilirubin, INR, or alkaline phosphatase. Liver enzyme changes occur most often during dose escalation, but may occur at any time during therapy.

Monitoring of liver function tests

Measure ALT, AST, alkaline phosphatase, total bilirubin, gamma-glutamyl transferase (gamma-GT) and serum albumin before initiation of treatment with Lojuxta. The medicinal product is contraindicated in patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests. If the baseline liver-related tests are abnormal, consider initiating the medicinal product after appropriate investigation by a hepatologist and the baseline abnormalities are explained or resolved.

During the first year, measure liver-related tests (ALT and AST, at a minimum) prior to each increase in dose or monthly, whichever occurs first. After the first year, do these tests at least every 3 months and before any increase in dose. Decrease the dose of Lojuxta if elevations of aminotransferase are observed and discontinue treatment for persistent or clinically significant elevations (see Table 1 for specific recommendations).

Dose modification based on elevated hepatic aminotransferases

Table 1 summarizes recommendations for dose adjustment and monitoring for patients who develop elevated aminotransferase during therapy with Lojuxta.

**Table 1: Dose Adjustment and Monitoring for Patients with Elevated Aminotransferases**

| ALT or AST | Treatment and monitoring recommendations* |
|---|---|
| ≥3x and <5x Upper Limit of Normal (ULN) | • Confirm elevation with a repeat measurement within one week.<br>• If confirmed, reduce the dose and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR).<br>• Repeat tests weekly and withhold dosing if there are signs of abnormal liver function (increase in bilirubin or INR), if aminotransferase levels rise above 5x ULN, or if aminotransferase levels do not fall below 3x ULN within approximately 4 weeks. Refer patients with persistent elevations in aminotransferase >3x ULN to a hepatologist for further investigation.<br>• If resuming Lojuxta after aminotransferase levels resolve to <3x ULN, consider reducing the dose and monitor liver-related tests more frequently. |
| ≥5x ULN | • Withhold dosing and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR). If aminotransferase levels do not fall below 3x ULN within approximately 4 weeks refer the patient to a hepatologist for further investigation.<br>• If resuming Lojuxta after aminotransferase levels 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 aminotransferase 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 Lojuxta and refer the patient to a hepatologist for further investigation.

Reintroduction of treatment may be considered if the benefits are considered to outweigh the risks associated with potential liver disease.

Hepatic steatosis and risk of progressive liver disease

Consistent with the mechanism of action of lomitapide, most treated patients exhibited increases in hepatic fat content. In an open-label Phase 3 study, 18 of 23 patients with HoFH developed hepatic steatosis (hepatic fat >5.56%) as measured by nuclear magnetic resonance spectroscopy (MRS) (see section 5.1). The median absolute increase in hepatic fat was 6% after both 26 weeks and 78 weeks of treatment, from 1% at baseline, measured by MRS. Hepatic steatosis is a risk factor for progressive liver disease including steatohepatitis and cirrhosis. The long term consequences of hepatic steatosis associated with Lojuxta treatment are unknown. Clinical data suggest that hepatic fat accumulation is reversible after stopping treatment with Lojuxta, but whether histological sequelae remain is unknown, especially after long-term use.

Monitoring for evidence of progressive liver disease.

Regular screening for steatohepatitis/fibrosis should be performed at baseline and on an annual basis using the following imaging and biomarker evaluations:

- Imaging for tissue elasticity, e.g. Fibroscan, acoustic radiation force impulse (ARFI), or magnetic resonance (MR) elastography

- Gamma-GT and serum albumin to detect possible liver injury

- At least one marker from each of the following categories:

    - High sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), CK-18 Fragment, NashTest (liver inflammation)
    - Enhanced Liver Fibrosis (ELF) panel, Fibrometer, AST/ALT ratio, Fib-4 score, Fibrotest (liver fibrosis)

The performance of these tests and their interpretation should involve collaboration between the treating physician and the hepatologist. Patients with results suggesting the presence of steatohepatitis or fibrosis should be considered for liver biopsy.

If a patient has biopsy-proven steatohepatitis or fibrosis, the benefit-risk should be reassessed and treatment stopped if necessary.

Dehydration

Post-marketing reports of dehydration and hospitalisation in patients treated with lomitapide have been reported. Patients treated with lomitapide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Concomitant use of CYP3A4 inhibitors

Lomitapide appears to be a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with Lojuxta is contraindicated (see section 4.3). In the lomitapide clinical trials, one patient with HoFH developed markedly elevated aminotransferase (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, Lojuxta should be stopped during the course of treatment.

Weak CYP3A4 inhibitors are expected to increase the exposure of lomitapide when taken simultaneously. When administered with atorvastatin, the dose of Lojuxta should either be taken 12 hours apart or be decreased by half (see section 4.2). The dose of Lojuxta should be administered 12 hours apart from any other weak CYP3A4 inhibitor.

Concomitant use of CYP3A4 inducers

Medicines that induce CYP3A4 would be expected to increase the rate and extent of metabolism of lomitapide. CYP3A4 inducers exert their effect in a time-dependent manner, and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2 weeks to decline.

Co-administration of a CYP3A4 inducer is expected to reduce the effect of Lojuxta. Any impact on efficacy is likely to be variable. When co-administering CYP3A4 inducers (i.e. aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, glucocorticoids, modafinil and phenytoin) with Lojuxta, the possibility of a drug-drug interaction affecting efficacy should be considered. The use of St. John’s Wort should be avoided with Lojuxta.

It is recommended to increase the frequency of LDL-C assessment during such concomitant use and consider increasing the dose of Lojuxta to ensure maintenance of the desired level of efficacy if the CYP3A4 inducer is intended for chronic use. On withdrawal of a CYP3A4 inducer, the possibility of increased exposure should be considered and a reduction in the dose of Lojuxta may be necessary.

Concomitant use of HMG-CoA reductase inhibitors ('statins')

Lomitapide increases plasma concentrations of statins. Patients receiving Lojuxta as adjunctive therapy to a statin should be monitored for adverse events that are associated with the use of high doses of statins. Statins occasionally cause myopathy. In rare cases, myopathy may take the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and can lead to fatality. All patients receiving Lojuxta in addition to a statin should be advised of the potential increased risk of myopathy and told to report promptly any unexplained muscle pain, tenderness, or weakness. Doses of simvastatin >40 mg should not be used with Lojuxta (see section 4.3).

Grapefruit juice

Grapefruit juice must be omitted from the diet while patients are treated with Lojuxta.

Risk of supratherapeutic or subtherapeutic anticoagulation with coumarin based anticoagulants

Lomitapide increases the plasma concentrations of warfarin. Increases in the dose of Lojuxta may lead to supratherapeutic anticoagulation, and decreases in the dose may lead to subtherapeutic anticoagulation. Difficulty controlling INR contributed to early discontinuation from the Phase 3 trial for one of five patients taking concomitant warfarin. Patients taking warfarin should undergo regular monitoring of the INR, especially after any changes in Lojuxta dosage. The dose of warfarin should be adjusted as clinically indicated.

Use of alcohol

Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. In the Phase 3 trial, 3 of 4 patients with ALT elevations >5x ULN reported alcohol consumption beyond the limits recommended in the protocol. The use of alcohol during Lojuxta treatment is not recommended.

Hepatotoxic agents

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

Reduced absorption of fat-soluble vitamins and serum fatty acids

Given its mechanism of action in the small intestine, lomitapide may reduce the absorption of fat-soluble nutrients. In the Phase 3 trial, patients were provided daily dietary supplements of vitamin E, linoleic acid, ALA, EPA and 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 lomitapide treatment of up to 78 weeks. Patients treated with Lojuxta should take daily supplements that contain 400 international units vitamin E and approximately 200 mg linoleic acid, 210 mg ALA, 110 mg EPA, and 80 mg DHA.

Contraception measures in women of child-bearing potential

Before initiating treatment in women of child-bearing potential, appropriate advice on effective methods of contraception should be provided, and effective contraception initiated. Patients taking oestrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting (see section 4.5). Oestrogen-containing oral contraceptives are weak CYP3A4 inhibitors (see section 4.2).

Patients should be advised to immediately contact their physician and stop taking Lojuxta if they become pregnant (see section 4.6).

Lactose

Lojuxta contains lactose and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption.

## 4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on Lojuxta and other forms of interaction

**Table 2: Interactions between Lojuxta and other medicinal products and other forms of interaction**

| Medicinal products | Effects on lomitapide levels | Recommendation concerning co-administration with Lojuxta |
|---|---|---|
| Inhibitors of CYP3A4 | When lomitapide 60 mg was co-administered with ketoconazole 200 mg twice daily, a strong inhibitor of CYP3A4, lomitapide AUC increased approximately 27-fold and $C_{max}$ increased approximately 15-fold.<br><br>Interactions between moderate CYP3A4 inhibitors and lomitapide have not been studied.<br><br>Moderate CYP3A4 inhibitors are predicted to have a substantial impact on lomitapide's pharmacokinetics. Concomitant use of moderate CYP3A4 inhibitors are expected to increase lomitapide exposure by 4-10 fold based on the results of the study with the strong CYP3A4 inhibitor ketoconazole and on historical data for the model CYP3A4 probe midazolam.<br><br>Weak CYP3A4 inhibitors are expected to increase the exposure of lomitapide when taken simultaneously.<br><br>When lomitapide 20 mg was co-administered simultaneously with atorvastatin, a weak CYP3A4 inhibitor, lomitapide AUC and $C_{max}$ increased approximately 2-fold. When the dose of lomitapide was taken 12 hours apart from atorvastatin, | Use of strong or moderate inhibitors of CYP3A4 is contraindicated with Lojuxta. If treatment with antifungal azoles (e.g., itraconazole, ketoconazole, fluconazole, voriconazole, posaconazole); the antiarrhythmic dronedarone; macrolide antibiotics (e.g., erythromycin, clarithromycin); ketolide antibiotics (e.g., telithromycin); HIV protease inhibitors; the calcium channel blockers diltiazem and verapamil is unavoidable, therapy with Lojuxta should be suspended during the course of treatment (see sections 4.3 and 4.4).<br><br>Grapefruit juice is a moderate inhibitor of CYP3A4 and is expected to substantially increase exposure to lomitapide. Patients taking Lojuxta should avoid consumption of grapefruit juice.<br><br>When administered with atorvastatin, the dose of Lojuxta should either be taken 12 hours apart or be decreased by half (see section 4.2). The dose of Lojuxta should be taken 12 hours apart from any other concomitant weak CYP3A4 inhibitors. Examples of weak CYP3A4 inhibitors include: alprazolam, amiodarone, amlodipine, atorvastatin, azithromycin, bicalutamide, cilostazol, cimetidine, ciclosporin, clotrimazole, fluoxetine, fluvoxamine, fosaprepitant, ginkgo, goldenseal, isoniazid, ivacaftor, lacidipine, lapatinib, linagliptin, nilotinib, oestrogen-containing oral contraceptives, pazopanib, peppermint oil, propiverine, ranitidine, ranolazine, roxithromycin, Seville oranges, tacrolimus, ticagrelor and tolvaptan. This |

| Medicinal products | Effects on lomitapide levels | Recommendation concerning co-administration with Lojuxta |
|---|---|---|
| | no clinically meaningful increase in lomitapide exposure was observed.<br><br>When lomitapide 20 mg was co-administered simultaneously or 12 hours apart with ethinyl estradiol/norgestimate, a weak CYP3A4 inhibitor, no clinically meaningful increase in lomitapide exposure was observed. | list is not intended to be comprehensive and prescribers should check the prescribing information of drugs to be co-administered with Lojuxta for potential CYP3A4 mediated interactions.<br><br>The effect of administration of more than one weak CYP3A4 inhibitor has not been tested, but the effect on the exposure of lomitapide is expected to be greater than for co-administration of the individual inhibitors with lomitapide.<br><br>Exercise additional caution if administering more than 1 weak CYP3A4 inhibitor with Lojuxta. |
| Inducers of CYP3A4 | Medicines that induce CYP3A4 would be expected to increase the rate and extent of metabolism of lomitapide. Consequently, this would reduce the effect of lomitapide. Any impact on efficacy is likely to be variable. | When co-administering CYP3A4 inducers (i.e., aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, St John's Wort, glucocorticoids, modafinil and phenytoin) with Lojuxta, the possibility of a drug-drug interaction affecting efficacy should be considered. It is recommended to increase the frequency of LDL-C assessment during such concomitant use and consider increasing the dose of Lojuxta to ensure maintenance of the desired level of efficacy if the CYP3A4 inducer is intended for chronic use. |
| Bile acid sequestrants | Lomitapide has not been tested for interaction with bile acid sequestrants (resins such as colesevelam and cholestyramine). | Because bile acid sequestrants can interfere with the absorption of oral medicines, bile acid sequestrants should be taken at least 4 hours before or at least 4 hours after Lojuxta. |

Effects of lomitapide on other medicinal products

*HMG-CoA Reductase Inhibitors ("Statins"):* Lomitapide increases plasma concentrations of statins. When lomitapide 60 mg was administered to steady state prior to simvastatin 40 mg, simvastatin acid AUC and $C_{max}$ increased 68% and 57%, respectively. When lomitapide 60 mg was administered to steady state prior to atorvastatin 20 mg, atorvastatin acid AUC and $C_{max}$ increased 52% and 63%, respectively. When lomitapide 60 mg was administered to steady state prior to rosuvastatin 20 mg, rosuvastatin $T_{max}$ increased from 1 to 4 hours, AUC was increased 32%, and its $C_{max}$ was unchanged. The risk of myopathy with simvastatin is dose related. Use of Lojuxta is contraindicated in patients treated with high doses of simvastatin (>40 mg) (see sections 4.3 and 4.4).

*Coumarin anticoagulants:* When lomitapide 60 mg was administered to steady state and 6 days following warfarin 10 mg, INR increased 1.26-fold. AUCs for R(+)-warfarin and S(-)-warfarin increased 25% and 30%, respectively. $C_{max}$ for R(+)-warfarin and S(-)-warfarin increased 14% and 15%, respectively. In patients taking coumarins (such as warfarin) and Lojuxta concomitantly, INR

should be determined before starting Lojuxta and monitored regularly with dosage of coumarins adjusted as clinically indicated (see section 4.4).

*Fenofibrate, niacin and ezetimibe*: When lomitapide was administered to steady state prior to micronised fenofibrate 145 mg, extended release niacin 1000 mg, or ezetimibe 10 mg, no clinically significant effects on the exposure of any of these medicinal products were observed. No dose adjustments are required when co-administered with Lojuxta.

*Oral contraceptives:* When lomitapide 50 mg was administered to steady state along with an oestrogen-based oral contraceptive, no clinically meaningful or statistically significant impact on the pharmacokinetics of the components of the oral contraceptive (ethinyl estradiol and 17-deacetyl norgestimate, the metabolite of norgestimate) was observed. Lomitapide is not expected to directly influence the efficacy of oestrogen based oral contraceptives; however diarrhoea and/or vomiting may reduce hormone absorption. In cases of protracted or severe diarrhoea and/or vomiting lasting more than 2 days, additional contraceptive measures should be used for 7 days after resolution of symptoms.

*P-gp substrates:* Lomitapide inhibits P-gp *in vitro*, and may increase the absorption of P-gp substrates. Coadministration of Lojuxta 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 Lojuxta.

*In vitro assessment of drug interactions*: Lomitapide inhibits CYP3A4. Lomitapide does not induce CYPs 1A2, 3A4, or 2B6, and does not inhibit CYPs 1A2, 2B6, 2C9, 2C19, 2D6, or 2E1. Lomitapide is not a P-gp substrate but does inhibit P-gp. Lomitapide does not inhibit breast cancer resistance protein (BCRP).

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Lojuxta is contraindicated during pregnancy. There are no reliable data on its use in pregnant women. Animal studies have shown developmental toxicity (teratogenicity, embryotoxicity, see section 5.3). The potential risk for humans is unknown.

Use in women of child-bearing potential

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. Patients taking oestrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting. Additional contraceptive measures should be used until resolution of symptoms (see section 4.5).

Breast-feeding

It is not known whether lomitapide is excreted into human milk. Because of the potential for adverse effects based on findings in animal studies with lomitapide (see section 5.3), a decision should be made whether to discontinue breast-feeding or discontinue the medicinal product, taking into account the importance of the medicinal product to the mother.

Fertility

No adverse effects on fertility were observed in male and female rats administered lomitapide at systemic exposures (AUC) estimated to be 4 to 5 times higher than in humans at the maximum recommended human dose (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Lojuxta may have a minor influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile

The most serious adverse reactions during treatment were liver aminotransferase abnormalities (see section 4.4).

The most common adverse reactions were gastrointestinal effects. Gastrointestinal adverse reactions were reported by 27 (93%) of 29 patients in the Phase 3 clinical trial. Diarrhoea 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. Gastrointestinal adverse reactions occurred more frequently during the dose escalation phase of the study and decreased once patients established the maximum tolerated dose of lomitapide.

Gastrointestinal adverse reactions of severe intensity were reported by 6 (21%) of 29 patients in the Phase 3 clinical trial, with the most common being diarrhoea (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.

The most commonly reported adverse reactions of severe intensity were diarrhoea (4 subjects, 14%), vomiting (3 patients, 10%), and abdominal distension and ALT increased (2 subjects each, 7%).

Tabulated list of adverse reactions

Frequency of the adverse reactions is defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 3 lists all adverse reactions reported across the 35 patients treated in the Phase 2 Study UP1001 and in the Phase 3 Study UP1002/AEGR-733-005 or its extension study AEGR-733-012.

**Table 3: Frequency of Adverse Reactions in HoFH Patients**

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| Infections and infestations | Common | Gastroenteritis |
| Metabolism and nutrition disorders | Very common | Decreased appetite |
| | Not known | Dehydration |
| Nervous system disorders | Common | Dizziness<br>Headache<br>Migraine |
| Gastrointestinal disorders | Very common | Diarrhoea<br>Nausea<br>Vomiting<br>Abdominal discomfort<br>Dyspepsia<br>Abdominal pain<br>Abdominal pain upper<br>Flatulence<br>Abdominal distension<br>Constipation |
| | Common | Gastritis<br>Rectal tenesmus<br>Aerophagia<br>Defaecation urgency<br>Eructation<br>Frequent bowel movements<br>Gastric dilatation<br>Gastric disorder<br>Gastrooesophageal reflux disease<br>Haemorrhoidal haemorrhage<br>Regurgitation |
| Hepatobiliary disorders | Common | Hepatic steatosis<br>Hepatotoxicity<br>Hepatomegaly |
| Skin and subcutaneous tissue disorders | Common | Ecchymosis<br>Papule<br>Rash erythematous<br>Xanthoma |
| | Not known | Alopecia |
| Musculoskeletal and connective tissue disorders | Not known | Myalgia |
| General disorders and administration site conditions | Common | Fatigue |
| Investigations | Very common | Alanine aminotransferase increased<br>Aspartate aminotransferase increased<br>Weight decreased |
| | Common | International normalised ratio increased<br>Blood alkaline phosphatase increased<br>Blood potassium decreased<br>Carotene decreased<br>International normalised ratio abnormal<br>Liver function test abnormal<br>Prothrombin time prolonged<br>Transaminases increased<br>Vitamin E decreased<br>Vitamin K decreased |

Table 4 lists all adverse reactions for subjects who received lomitapide monotherapy (N=291) treated in Phase 2 studies in subjects with elevated LDL-C (N=462).

**Table 4: Frequency of Adverse Reactions in Elevated LDL-C Patients**

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| Infections and infestations | Uncommon | Gastroenteritis<br>Gastrointestinal infection<br>Influenza<br>Nasopharyngitis<br>Sinusitis |
| Blood and lymphatic system disorders | Uncommon | Anaemia |
| Metabolism and nutrition disorders | Common | Decreased appetite |
| | Uncommon | Dehydration<br>Increased appetite |
| Nervous system disorders | Uncommon | Paraesthesia<br>Somnolence |
| Eye disorders | Uncommon | Eye swelling |
| Ear and labyrinth disorders | Uncommon | Vertigo |
| Respiratory, thoracic and mediastinal disorders | Uncommon | Pharyngeal lesion<br>Upper-airway cough syndrome |
| Gastrointestinal disorders | Very common | Diarrhoea<br>Nausea<br>Flatulence |
| | Common | Abdominal pain upper<br>Abdominal distension<br>Abdominal pain<br>Vomiting<br>Abdominal discomfort<br>Dyspepsia<br>Eructation<br>Abdominal pain lower<br>Frequent bowel movements |
| | Uncommon | Dry mouth<br>Faeces hard<br>Gastrooeosophageal reflux disease<br>Abdominal tenderness<br>Epigastric discomfort<br>Gastric dilatation<br>Haematemesis<br>Lower gastrointestinal haemorrhage<br>Reflux oesophagitis |
| Hepatobiliary disorders | Uncommon | Hepatomegaly |
| Skin and subcutaneous tissue disorders | Uncommon | Blister<br>Dry skin<br>Hyperhidrosis |
| Musculoskeletal and connective tissue disorders | Common | Muscle spasms |
| | Uncommon | Arthralgia<br>Myalgia<br>Pain in extremity<br>Joint swelling<br>Muscle twitching |
| Renal and urinary disorders | Uncommon | Haematuria |

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| General disorders and administrative site conditions | Common | Fatigue<br>Asthenia |
| | Uncommon | Chest pain<br>Chills<br>Early satiety<br>Gait disturbance<br>Malaise<br>Pyrexia |
| Investigations | Common | Alanine aminotransferase increased<br>Aspartate aminotransferase increased<br>Hepatic enzyme increased<br>Liver function test abnormal<br>Neutrophil count decreased<br>White blood cell count decreased |
| | Uncommon | Weight decreased<br>Blood bilirubin increased<br>Gamma-glutamyltransferase increased<br>Neutrophil percentage increased<br>Protein urine<br>Prothrombin time prolonged<br>Pulmonary function test abnormal<br>White blood cell count increased |

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

There is no specific treatment in the event of overdose. In rodents, single oral doses of lomitapide ≥600 times higher than the maximum recommended human dose (1 mg/kg) were well tolerated. The maximum dose administered to human subjects in clinical studies was 200 mg as a single dose; there were no adverse reactions.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other lipid modifying agents, plain. ATC code: C10AX12

Mechanism of action

Lomitapide is a selective inhibitor of microsomal 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 reduces lipoprotein secretion and circulating concentrations of lipoprotein-borne lipids including cholesterol and triglycerides.

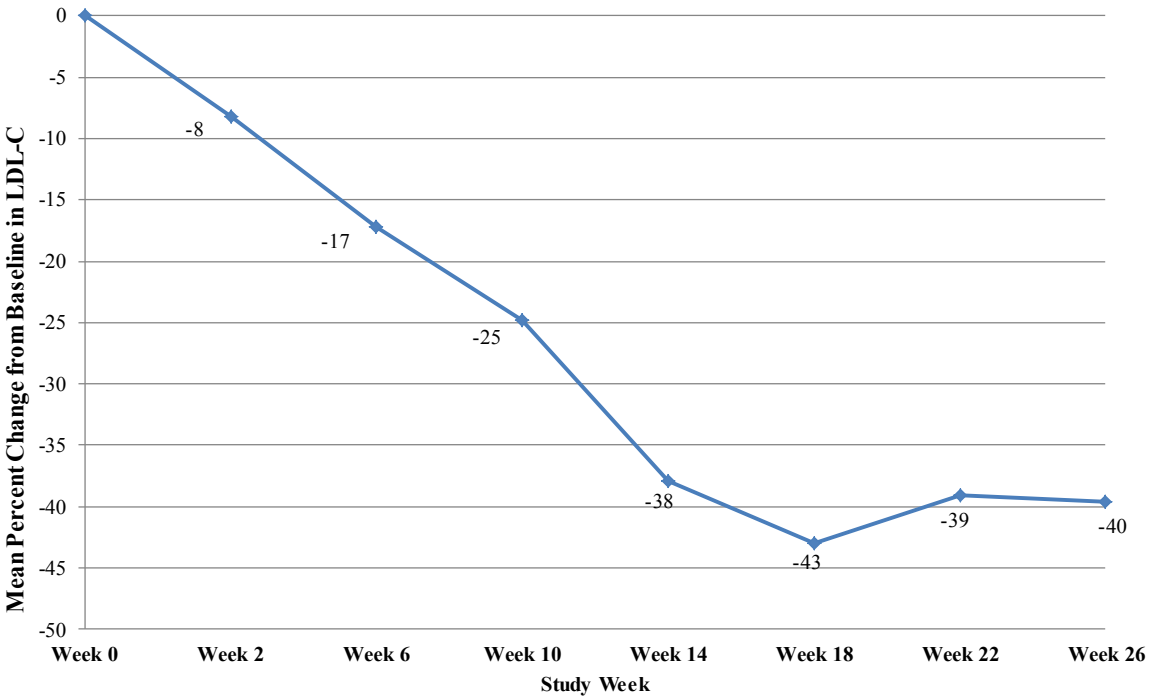
Clinical efficacy and safety

A single arm, open-label study (UP1002/AEGR-733-005) evaluated the efficacy and safety of lomitapide when co-administered with a low-fat diet and other lipid-lowering therapies in adult

patients with HoFH. Patients were instructed to maintain a low-fat diet (<20% calories from fat) and their lipid-lowering therapies at study entry, including apheresis if applicable, from 6 weeks prior to baseline through at least Week 26. The dose of lomitapide was escalated from 5 mg to an individually determined maximum tolerated dose up to 60 mg. After Week 26, patients remained on lomitapide to determine the effects of longer-term treatment and were allowed to change background lipid-lowering therapies. The study provided for a total of 78 weeks of treatment.

Twenty-nine patients were enrolled, of whom 23 completed through Week 78. Sixteen males (55%) and 13 females (45%) were included with a mean age of 30.7 years, ranging from 18 to 55 years. The mean dose of lomitapide was 45 mg at Week 26 and 40 mg at Week 78. At Week 26, the mean percent change in LDL-C from baseline of LDL-C was -40% ($p<0.001$) in the Intent to Treat (ITT) population. Mean percent change from baseline through Week 26 using last observation carried forward (LOCF) to each assessment is shown in Figure 1.

**Figure 1: Mean percent changes from baseline in LDL-C in the major effectiveness study UP1002/AEGR-733-005 through Week 26 (the Primary Endpoint) using LOCF to each assessment (N=29)**




Changes in lipids and lipoproteins through Week 26 and Week 78 of lomitapide treatment are presented in Table 5.

**Table 5: Absolute values and percent changes from baseline to Weeks 26 and 78 in lipids and lipoproteins (major effectiveness study UP1002/AEGR-733-005)**

| Parameter (units) | Baseline | Week 26/LOCF (N=29) | | | Week 78 (N=23) | | |
|---|---|---|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | % Change | p-value[b] | Mean (SD) | % Change | p-value[b] |
| LDL-C, direct (mg/dL) | 336 (114) | 190 (104) | -40 | <0.001 | 210 (132) | -38 | <0.001 |
| Total Cholesterol (TC) (mg/dL) | 430 (135) | 258 (118) | -36 | <0.001 | 281 (149) | -35 | <0.001 |
| Apolipoprotein B (apo B) (mg/dL) | 259 (80) | 148 (74) | -39 | <0.001 | 151 (89) | -43 | <0.001 |
| Triglycerides (TG) (mg/dL)[a] | 92 | 57 | -45 | 0.009 | 59 | -42 | 0.012 |
| Non high-density lipoprotein cholesterol (Non-HDL-C) (mg/dL) | 386 (132) | 217 (113) | -40 | <0.001 | 239 (146) | -39 | <0.001 |
| Very-low-density lipoprotein cholesterol (VLDL-C) (mg/dL) | 21 (10) | 13 (9) | -29 | 0.012 | 16 (15) | -31 | 0.013 |
| Lipoprotein (a) (Lp(a)) (nmol/L)[a] | 66 | 61 | -13 | 0.094 | 72 | -4 | <0.842 |
| High-density lipoprotein cholesterol (HDL-C) (mg/dL) | 44 (11) | 41 (13) | -7 | 0.072 | 43 (12) | -4.6 | 0.246 |

[a] Median presented for TG and Lp(a). p-value is based on the mean percent change
[b] p-value on the mean percent change from baseline based on paired t-test

At both Week 26 and Week 78, there were significant reductions in LDL-C, TC, apo B, TG, non-HDL-C, VLDL-C and changes in HDL-C trended lower at Week 26 and returned to baseline levels by Week 78.

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

At baseline, 93% were on a statin, 76% were on ezetimibe, 10% on niacin, 3% on a bile acid sequestrant and 62% were receiving apheresis. Fifteen of 23 (65%) patients had their lipid-lowering treatment reduced by Week 78, including planned and unplanned reductions/interruptions. Apheresis was discontinued in 3 out of 13 patients who were on it at Week 26, and frequency was reduced in 3 patients while maintaining low LDL-C levels through Week 78. The clinical benefit of reductions in background lipid-lowering therapy, including apheresis, is not certain.

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 and 1 having LDL-C <70 mg/dL at that time point.

In this study, 10 patients experienced elevations in AST and/or ALT >3 x ULN (see Table 6).

**Table 6: Highest liver function test results post first dose (major effectiveness study UP1002/AEGR-733-005)**

| Parameter/Abnormality | N (%) |
|---|---|
| ALT | |
| Number of Patients with Assessments | 29 |
| >3 to ≤5 x ULN | 6 (20.7) |
| >5 to ≤10 x ULN | 3 (10.3) |
| >10 to ≤20 x ULN | 1 (3.4) |
| >20 x ULN | 0 |
| AST | |
| Number of Patients with Assessments | 29 |
| >3 to ≤5 x ULN | 5 (17.2) |
| >5 to ≤10 x ULN | 1 (3.4) |
| >10 to ≤20 x ULN | 0 |
| >20 x ULN | 0 |

Elevations in ALT and/or AST >5 x ULN were managed with a dose reduction or temporary suspension of lomitapide dosing, and all patients were able to continue with study drug treatment. No clinically meaningful elevations in total bilirubin or alkaline phosphatase were observed. Hepatic fat was prospectively measured using MRS in all eligible patients during the clinical trial (Table 7). Data from individuals who had repeat measurements after stopping lomitapide show that hepatic fat accumulation is reversible, but whether histological sequelae remain is unknown.

**Table 7: Maximum categorical changes in % hepatic fat (major effectiveness study UP1002/AEGR-733-005)**

| 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) |

The European Medicines Agency has deferred the obligation to submit the results of studies with Lojuxta in one or more subsets of the paediatric population in HoFH (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption

The absolute oral bioavailability of lomitapide is 7%. Absorption is not limited by penetration of the drug across the intestinal barrier but is predominantly influenced by an extensive first pass effect. Peak plasma concentrations of lomitapide were reached 4-8 hours following oral dosing. Lomitapide pharmacokinetics is approximately dose-proportional for oral single doses in the therapeutic range. Doses higher than 60 mg suggest a trend toward nonlinearity and are not recommended.

Upon multiple dosing $C_{max}$ and AUC increased in approximate proportion to lomitapide dose. $C_{max}$ and AUC were increased following either a high-fat meal (77% and 58%, respectively) or low fat meal (70% and 28%, respectively). Accumulation of lomitapide in plasma was consistent with that predicted after a single dose following once daily oral dosing above 25 mg for up to 4 weeks. Inter-individual variability in lomitapide AUC was approximately 50%.

At steady state the accumulation of lomitapide was 2.7 at 25 mg and 3.9 at 50 mg.

Distribution

Following intravenous administration, the volume of distribution of lomitapide was high (mean=1200 litres) despite a high degree (>99.8%) of binding to plasma protein. In animal studies lomitapide was highly concentrated (200-fold) in the liver.

Biotransformation

Lomitapide is extensively metabolised, predominantly by CYP3A4. CYP isoforms 2E1, 1A2, 2B6, 2C8, and 2C19 are involved to a lesser extent and isoforms 2D6 and 2C9 are not involved in the metabolism of lomitapide.

Elimination

Following administration of a radiolabeled oral solution dose to healthy subjects, 93% of the administered dose was recovered in urine and faeces. Approximately 33% of the radioactivity was excreted in urine as metabolites. The remainder was excreted in faeces, primarily as oxidised metabolites. The elimination half-life of lomitapide was approximately 29 hours.

Special populations

Data in the pivotal clinical trial were analyzed with respect to the impact of potential covariates on lomitapide exposure. Of the parameters examined (race, body mass index (BMI), gender, weight, age), only BMI could be classified as a potential covariate.

*Age and gender*

There was no clinically relevant effect of age (18-64 years) or gender on the pharmacokinetics of lomitapide.

*Race*

No dose adjustment is required for Caucasian or Latino patients. There is insufficient information to determine if Lojuxta requires dose adjustment in other races. However, since the medicinal product is dosed in an escalating fashion according to individual patient safety and tolerability, no adjustment to the dosing regimen is recommended based on race.

*Renal insufficiency*

In the renal impairment population, lomitapide was only studied in patients with end-stage renal disease (ESRD). A pharmacokinetic study in patients with ESRD undergoing hemodialysis demonstrated a 36% increase in mean lomitapide plasma concentration compared to matched healthy controls. The terminal half-life of lomitapide was not affected.

*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. Lojuxta has not been studied in patients with severe hepatic impairment (Child-Pugh score 10-15).

*Paediatric population*

Lojuxta has not been investigated in children less than 18 years of age.

*Elderly population*

Lojuxta has not been investigated in patients aged 65 years or older.

## 5.3 Preclinical safety data

In repeat-dose oral toxicology studies in rodents and dogs, the principal drug-related findings were lipid accumulation in the small intestine and/or liver associated with decreases in serum cholesterol and/or triglyceride levels. These changes are secondary to the mechanism of action of lomitapide. Other liver-related changes in repeat-dose toxicity studies in rats and dogs included increased serum aminotransferases, subacute inflammation (rats only), and single-cell necrosis. In a 1 year repeat-dose study in dogs there were no microscopic changes in the liver although serum AST was minimally increased in females.

Pulmonary histiocytosis was observed in rodents. Decreased red blood cell parameters as well as poikilocytosis and/or anisocytosis were observed in dogs. Testicular toxicity was observed in dogs at 205 times the human exposure (AUC) at 60 mg in a 6-month study. No adverse effects on the testes were observed in a 1-year study in dogs at 64 times the human exposure at 60 mg.

In a dietary carcinogenicity study in mice, lomitapide was administered up to 104 weeks at doses ranging from 0.3 to 45 mg/kg/day. There were statistically significant increases in the incidences of liver adenoma and carcinoma at doses ≥1.5 mg/kg/day in males (≥ 2 times the human exposure at 60 mg daily based on AUC) and ≥7.5 mg/kg/day in females (≥ 9 times the human exposure at 60 mg based on AUC). Incidences of small intestinal carcinoma and/or combined adenoma and carcinoma (rare tumours in mice) were significantly increased at doses ≥15 mg/kg/day in males (≥ 26 times the human exposure at 60 mg based on AUC) and at 15 mg/kg/day in females (22 times the human exposure at 60 mg based on AUC).

In an oral carcinogenicity study in rats, lomitapide was administered up to 99 weeks at doses up to 7.5 mg/kg/day in males and 2.0 mg/kg/day in females. Focal hepatic fibrosis was observed in males and females and hepatic cystic degeneration was observed in males only. In high-dose males, an increased incidence of pancreatic acinar cell adenoma was observed at an exposure 6 times that in humans at 60 mg based on AUC.

Lomitapide was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* studies.

Lomitapide had no effect on reproductive function in female rats at doses up to 1 mg/kg or in male rats at doses up to 5 mg/kg. Systemic exposures to lomitapide at these doses were estimated to be 4 times (females) and 5 times (males) higher than the human exposure at 60 mg based on AUC.

Lomitapide was teratogenic in rats in the absence of maternal toxicity at an exposure (AUC) estimated to be twice that in humans at 60 mg. There was no evidence of embryofoetal toxicity in rabbits at 3 times the maximum recommended human dose (MRHD) of 60 mg based on body surface area. Embryofoetal toxicity was observed in rabbits in the absence of maternal toxicity at ≥6.5 times the MRHD. In ferrets, lomitapide was both maternally toxic and teratogenic at <1 times the MRHD.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule content
Pregelatinised starch (maize)
Sodium starch glycolate
Microcrystalline cellulose
Lactose monohydrate
Silica, colloidal anhydrous
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)

Printing ink
Shellac
Black iron oxide (E172)
Propylene glycol

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years.

### 6.4 Special precautions for storage

Store below 30°C.
Keep the bottle tightly closed in order to protect from moisture.

### 6.5 Nature and contents of container

High density polyethylene (HDPE) bottle fitted with a polyester/aluminium foil/cardboard induction seal and polypropylene screw cap.

Package sizes are:
28 capsules

### 6.6 Special precautions for disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Aegerion Pharmaceuticals Ltd
Lakeside House
1 Furzeground Way
Stockley Park East
Uxbridge UB11 1BD
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/851/005

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Lojuxta 60 mg hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains lomitapide mesylate equivalent to 60 mg lomitapide.

Excipient with known effect
Each hard capsule contains 389.68 mg of lactose (as monohydrate) (see section 4.4).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Capsule, hard.

The capsule is a yellow cap/yellow body hard capsule of 23.4 mm, printed with black ink imprinted with “60 mg” on body and “A733” on cap.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Lojuxta is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH).

Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism) must be excluded.

### 4.2 Posology and method of administration

Treatment with Lojuxta should be initiated and monitored by a physician experienced in the treatment of lipid disorders.

Posology

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 to the maximum recommended dose of 60 mg (see section 4.8).

The dose should be escalated gradually to minimise the incidence and severity of gastrointestinal side effects and aminotransferase elevations.

Administration with food may increase exposure to Lojuxta. Lojuxta should be taken on an empty stomach, at least 2 hours after the evening meal because the fat content of a recent meal may adversely impact gastrointestinal tolerability.

The occurrence and severity of gastrointestinal adverse reactions associated with the use of Lojuxta decreases in the presence of a low fat diet. Patients should follow a diet supplying less than 20% of energy from fat prior to initiating Lojuxta treatment, and should continue this diet during treatment. Dietary counselling should be provided.

Patients should avoid consumption of grapefruit juice (see sections 4.4 and 4.5).

For patients on a stable maintenance dose of Lojuxta who receive atorvastatin either:

- Separate the dose of the medications by 12 hours

OR

- Decrease the dose of Lojuxta by half.

Patients on 5 mg should remain on 5 mg.
Careful titration may then be considered according to LDL-C response and safety/tolerability.
Upon discontinuation of atorvastatin the dose of Lojuxta should be up-titrated according to LDL-C response and safety/tolerability.

For patients on a stable maintenance dose of Lojuxta who receive any other weak CYP3A4 inhibitor, separate the dose of the medications (Lojuxta and the weak CYP3A4 inhibitor) by 12 hours.

Consider limiting the maximum dose of Lojuxta according to desired LDL-C response.
Exercise additional caution if administering more than 1 weak CYP3A4 inhibitor with Lojuxta.

Based on observations of decreased essential fatty acid and vitamin E levels in clinical trials, patients should take daily dietary supplements that provide 400 IU vitamin E and approximately 200 mg linoleic acid, 110 mg eicosapentaenoic acid (EPA), 210 mg alpha linolenic acid (ALA) and 80 mg docosahexaenoic acid (DHA) per day, throughout treatment with Lojuxta.

*Elderly population*

There is limited experience with Lojuxta in patients aged 65 years or older. Therefore, particular caution should be exercised in these patients.

Since the recommended dose regimen involves starting at the low end of the dosing range and escalating cautiously according to individual patient tolerability, no adjustment to the dosing regimen is recommended for the elderly.

*Hepatic impairment*

Lojuxta is contraindicated in patients with moderate or severe hepatic impairment including patients with unexplained persistent abnormal liver function tests (see section 5.2).

Patients with mild hepatic impairment (Child-Pugh A) should not exceed 40 mg daily.

*Renal impairment*

Patients with end-stage renal disease receiving dialysis should not exceed 40 mg daily (see section 5.2).

*Paediatric population*

The safety and efficacy of Lojuxta in children <18 years have not been established and the use of this medicinal product in children is therefore not recommended. No data are available.

Method of administration

Oral use.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests.
- Patients with a known significant or chronic bowel disease such as inflammatory bowel disease or malabsorption.
- Concomitant administration of >40 mg simvastatin (see section 4.5).
- Concomitant use of Lojuxta with strong or moderate cytochrome P450 (CYP) 3A4 inhibitors (e.g., antifungal azoles such as itraconazole, fluconazole,ketoconazole, voriconazole, posaconazole; macrolide antibiotics such as erythromycin or clarithromycin; ketolide antibiotics such as telithromycin; HIV protease inhibitors; the calcium channel blockers diltiazem and verapamil, and the anti-arrhythmic dronedarone [see section 4.5]).
- Pregnancy (see section 4.6).

## 4.4 Special warnings and precautions for use

Liver enzyme abnormalities and liver monitoring

Lomitapide can cause elevations in alanine aminotransferase [ALT] and aspartate aminotransferase [AST] and hepatic steatosis. The extent to which lomitapide-associated hepatic steatosis promotes the elevations in aminotransferase is unknown. Although cases of hepatic dysfunction (elevated aminotransferase with increase in bilirubin or International Normalized Ratio [INR]) or hepatic failure have not been reported, there is concern that lomitapide could induce steatohepatitis, which can progress to cirrhosis over several years. The clinical studies supporting the safety and efficacy of lomitapide in HoFH would have been unlikely to detect this adverse outcome given their size and duration.

Elevations in aminotransferases (ALT and/or AST) are associated with lomitapide (see section 5.1). There were no concomitant or subsequent clinically meaningful elevations in serum bilirubin, INR, or alkaline phosphatase. Liver enzyme changes occur most often during dose escalation, but may occur at any time during therapy.

Monitoring of liver function tests

Measure ALT, AST, alkaline phosphatase, total bilirubin, gamma-glutamyl transferase (gamma-GT) and serum albumin before initiation of treatment with Lojuxta. The medicinal product is contraindicated in patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests. If the baseline liver-related tests are abnormal, consider initiating the medicinal product after appropriate investigation by a hepatologist and the baseline abnormalities are explained or resolved.

During the first year, measure liver-related tests (ALT and AST, at a minimum) prior to each increase in dose or monthly, whichever occurs first. After the first year, do these tests at least every 3 months and before any increase in dose. Decrease the dose of Lojuxta if elevations of aminotransferase are observed and discontinue treatment for persistent or clinically significant elevations (see Table 1 for specific recommendations).

Dose modification based on elevated hepatic aminotransferases

Table 1 summarizes recommendations for dose adjustment and monitoring for patients who develop elevated aminotransferase during therapy with Lojuxta.

**Table 1: Dose Adjustment and Monitoring for Patients with Elevated Aminotransferases**

| ALT or AST | Treatment and monitoring recommendations* |
|---|---|
| ≥3x and <5x Upper Limit of Normal (ULN) | • Confirm elevation with a repeat measurement within one week.<br>• If confirmed, reduce the dose and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR).<br>• Repeat tests weekly and withhold dosing if there are signs of abnormal liver function (increase in bilirubin or INR), if aminotransferase levels rise above 5x ULN, or if aminotransferase levels do not fall below 3x ULN within approximately 4 weeks. Refer patients with persistent elevations in aminotransferase >3x ULN to a hepatologist for further investigation.<br>• If resuming Lojuxta after aminotransferase levels resolve to <3x ULN, consider reducing the dose and monitor liver-related tests more frequently. |
| ≥5x ULN | • Withhold dosing and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR). If aminotransferase levels do not fall below 3x ULN within approximately 4 weeks refer the patient to a hepatologist for further investigation.<br>• If resuming Lojuxta after aminotransferase levels 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 aminotransferase 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 Lojuxta and refer the patient to a hepatologist for further investigation.

Reintroduction of treatment may be considered if the benefits are considered to outweigh the risks associated with potential liver disease.

Hepatic steatosis and risk of progressive liver disease

Consistent with the mechanism of action of lomitapide, most treated patients exhibited increases in hepatic fat content. In an open-label Phase 3 study, 18 of 23 patients with HoFH developed hepatic steatosis (hepatic fat >5.56%) as measured by nuclear magnetic resonance spectroscopy (MRS) (see section 5.1). The median absolute increase in hepatic fat was 6% after both 26 weeks and 78 weeks of treatment, from 1% at baseline, measured by MRS. Hepatic steatosis is a risk factor for progressive liver disease including steatohepatitis and cirrhosis. The long term consequences of hepatic steatosis associated with Lojuxta treatment are unknown. Clinical data suggest that hepatic fat accumulation is reversible after stopping treatment with Lojuxta, but whether histological sequelae remain is unknown, especially after long-term use.

Monitoring for evidence of progressive liver disease.

Regular screening for steatohepatitis/fibrosis should be performed at baseline and on an annual basis using the following imaging and biomarker evaluations:

- Imaging for tissue elasticity, e.g. Fibroscan, acoustic radiation force impulse (ARFI), or magnetic resonance (MR) elastography

- Gamma-GT and serum albumin to detect possible liver injury

- At least one marker from each of the following categories:

    - High sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), CK-18 Fragment, NashTest (liver inflammation)
    - Enhanced Liver Fibrosis (ELF) panel, Fibrometer, AST/ALT ratio, Fib-4 score, Fibrotest (liver fibrosis)

The performance of these tests and their interpretation should involve collaboration between the treating physician and the hepatologist. Patients with results suggesting the presence of steatohepatitis or fibrosis should be considered for liver biopsy.

If a patient has biopsy-proven steatohepatitis or fibrosis, the benefit-risk should be reassessed and treatment stopped if necessary.

Dehydration

Post-marketing reports of dehydration and hospitalisation in patients treated with lomitapide have been reported. Patients treated with lomitapide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Concomitant use of CYP3A4 inhibitors

Lomitapide appears to be a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with Lojuxta is contraindicated (see section 4.3). In the lomitapide clinical trials, one patient with HoFH developed markedly elevated aminotransferase (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, Lojuxta should be stopped during the course of treatment.

Weak CYP3A4 inhibitors are expected to increase the exposure of lomitapide when taken simultaneously. When administered with atorvastatin, the dose of Lojuxta should either be taken 12 hours apart or be decreased by half (see section 4.2). The dose of Lojuxta should be administered 12 hours apart from any other weak CYP3A4 inhibitor.

Concomitant use of CYP3A4 inducers

Medicines that induce CYP3A4 would be expected to increase the rate and extent of metabolism of lomitapide. CYP3A4 inducers exert their effect in a time-dependent manner, and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2 weeks to decline.

Co-administration of a CYP3A4 inducer is expected to reduce the effect of Lojuxta. Any impact on efficacy is likely to be variable. When co-administering CYP3A4 inducers (i.e. aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, glucocorticoids, modafinil and phenytoin) with Lojuxta, the possibility of a drug-drug interaction affecting efficacy should be considered. The use of St. John’s Wort should be avoided with Lojuxta.

It is recommended to increase the frequency of LDL-C assessment during such concomitant use and consider increasing the dose of Lojuxta to ensure maintenance of the desired level of efficacy if the CYP3A4 inducer is intended for chronic use. On withdrawal of a CYP3A4 inducer, the possibility of increased exposure should be considered and a reduction in the dose of Lojuxta may be necessary.

Concomitant use of HMG-CoA reductase inhibitors ('statins')

Lomitapide increases plasma concentrations of statins. Patients receiving Lojuxta as adjunctive therapy to a statin should be monitored for adverse events that are associated with the use of high doses of statins. Statins occasionally cause myopathy. In rare cases, myopathy may take the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and can lead to fatality. All patients receiving Lojuxta in addition to a statin should be advised of the potential increased risk of myopathy and told to report promptly any unexplained muscle pain, tenderness, or weakness. Doses of simvastatin >40 mg should not be used with Lojuxta (see section 4.3).

Grapefruit juice

Grapefruit juice must be omitted from the diet while patients are treated with Lojuxta.

Risk of supratherapeutic or subtherapeutic anticoagulation with coumarin based anticoagulants

Lomitapide increases the plasma concentrations of warfarin. Increases in the dose of Lojuxta may lead to supratherapeutic anticoagulation, and decreases in the dose may lead to subtherapeutic anticoagulation. Difficulty controlling INR contributed to early discontinuation from the Phase 3 trial for one of five patients taking concomitant warfarin. Patients taking warfarin should undergo regular monitoring of the INR, especially after any changes in Lojuxta dosage. The dose of warfarin should be adjusted as clinically indicated.

Use of alcohol

Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. In the Phase 3 trial, 3 of 4 patients with ALT elevations >5x ULN reported alcohol consumption beyond the limits recommended in the protocol. The use of alcohol during Lojuxta treatment is not recommended.

Hepatotoxic agents

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

Reduced absorption of fat-soluble vitamins and serum fatty acids

Given its mechanism of action in the small intestine, lomitapide may reduce the absorption of fat-soluble nutrients. In the Phase 3 trial, patients were provided daily dietary supplements of vitamin E, linoleic acid, ALA, EPA and 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 lomitapide treatment of up to 78 weeks. Patients treated with Lojuxta should take daily supplements that contain 400 international units vitamin E and approximately 200 mg linoleic acid, 210 mg ALA, 110 mg EPA, and 80 mg DHA.

Contraception measures in women of child-bearing potential

Before initiating treatment in women of child-bearing potential, appropriate advice on effective methods of contraception should be provided, and effective contraception initiated. Patients taking oestrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting (see section 4.5). Oestrogen-containing oral contraceptives are weak CYP3A4 inhibitors (see section 4.2).

Patients should be advised to immediately contact their physician and stop taking Lojuxta if they become pregnant (see section 4.6).

Lactose

Lojuxta contains lactose and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption.

## 4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on Lojuxta and other forms of interaction

**Table 2: Interactions between Lojuxta and other medicinal products and other forms of interaction**

| Medicinal products | Effects on lomitapide levels | Recommendation concerning co-administration with Lojuxta |
|---|---|---|
| Inhibitors of CYP3A4 | When lomitapide 60 mg was co-administered with ketoconazole 200 mg twice daily, a strong inhibitor of CYP3A4, lomitapide AUC increased approximately 27-fold and $C_{max}$ increased approximately 15-fold.<br><br>Interactions between moderate CYP3A4 inhibitors and lomitapide have not been studied.<br><br>Moderate CYP3A4 inhibitors are predicted to have a substantial impact on lomitapide's pharmacokinetics. Concomitant use of moderate CYP3A4 inhibitors are expected to increase lomitapide exposure by 4-10 fold based on the results of the study with the strong CYP3A4 inhibitor ketoconazole and on historical data for the model CYP3A4 probe midazolam.<br><br>Weak CYP3A4 inhibitors are expected to increase the exposure of lomitapide when taken simultaneously.<br><br>When lomitapide 20 mg was co-administered simultaneously with atorvastatin, a weak CYP3A4 inhibitor, lomitapide AUC and $C_{max}$ increased approximately 2-fold. When the dose of lomitapide was taken 12 hours apart from atorvastatin, | Use of strong or moderate inhibitors of CYP3A4 is contraindicated with Lojuxta. If treatment with antifungal azoles (e.g., itraconazole, ketoconazole, fluconazole, voriconazole, posaconazole); the antiarrhythmic dronedarone; macrolide antibiotics (e.g., erythromycin, clarithromycin); ketolide antibiotics (e.g., telithromycin); HIV protease inhibitors; the calcium channel blockers diltiazem and verapamil is unavoidable, therapy with Lojuxta should be suspended during the course of treatment (see sections 4.3 and 4.4).<br><br>Grapefruit juice is a moderate inhibitor of CYP3A4 and is expected to substantially increase exposure to lomitapide. Patients taking Lojuxta should avoid consumption of grapefruit juice.<br><br>When administered with atorvastatin, the dose of Lojuxta should either be taken 12 hours apart or be decreased by half (see section 4.2). The dose of Lojuxta should be taken 12 hours apart from any other concomitant weak CYP3A4 inhibitors. Examples of weak CYP3A4 inhibitors include: alprazolam, amiodarone, amlodipine, atorvastatin, azithromycin, bicalutamide, cilostazol, cimetidine, ciclosporin, clotrimazole, fluoxetine, fluvoxamine, fosaprepitant, ginkgo, goldenseal, isoniazid, ivacaftor, lacidipine, lapatinib, linagliptin, nilotinib, oestrogen-containing oral contraceptives, pazopanib, peppermint oil, propiverine, ranitidine, ranolazine, roxithromycin, Seville oranges, tacrolimus, ticagrelor and tolvaptan. This |

| Medicinal products | Effects on lomitapide levels | Recommendation concerning co-administration with Lojuxta |
|---|---|---|
| | no clinically meaningful increase in lomitapide exposure was observed.<br><br>When lomitapide 20 mg was co-administered simultaneously or 12 hours apart with ethinyl estradiol/norgestimate, a weak CYP3A4 inhibitor, no clinically meaningful increase in lomitapide exposure was observed. | list is not intended to be comprehensive and prescribers should check the prescribing information of drugs to be co-administered with Lojuxta for potential CYP3A4 mediated interactions.<br><br>The effect of administration of more than one weak CYP3A4 inhibitor has not been tested, but the effect on the exposure of lomitapide is expected to be greater than for co-administration of the individual inhibitors with lomitapide.<br><br>Exercise additional caution if administering more than 1 weak CYP3A4 inhibitor with Lojuxta. |
| Inducers of CYP3A4 | Medicines that induce CYP3A4 would be expected to increase the rate and extent of metabolism of lomitapide. Consequently, this would reduce the effect of lomitapide. Any impact on efficacy is likely to be variable. | When co-administering CYP3A4 inducers (i.e., aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, St John's Wort, glucocorticoids, modafinil and phenytoin) with Lojuxta, the possibility of a drug-drug interaction affecting efficacy should be considered. It is recommended to increase the frequency of LDL-C assessment during such concomitant use and consider increasing the dose of Lojuxta to ensure maintenance of the desired level of efficacy if the CYP3A4 inducer is intended for chronic use. |
| Bile acid sequestrants | Lomitapide has not been tested for interaction with bile acid sequestrants (resins such as colesevelam and cholestyramine). | Because bile acid sequestrants can interfere with the absorption of oral medicines, bile acid sequestrants should be taken at least 4 hours before or at least 4 hours after Lojuxta. |

Effects of lomitapide on other medicinal products

*HMG-CoA Reductase Inhibitors ("Statins"):* Lomitapide increases plasma concentrations of statins. When lomitapide 60 mg was administered to steady state prior to simvastatin 40 mg, simvastatin acid AUC and $C_{max}$ increased 68% and 57%, respectively. When lomitapide 60 mg was administered to steady state prior to atorvastatin 20 mg, atorvastatin acid AUC and $C_{max}$ increased 52% and 63%, respectively. When lomitapide 60 mg was administered to steady state prior to rosuvastatin 20 mg, rosuvastatin $T_{max}$ increased from 1 to 4 hours, AUC was increased 32%, and its $C_{max}$ was unchanged. The risk of myopathy with simvastatin is dose related. Use of Lojuxta is contraindicated in patients treated with high doses of simvastatin (>40 mg) (see sections 4.3 and 4.4).

*Coumarin anticoagulants:* When lomitapide 60 mg was administered to steady state and 6 days following warfarin 10 mg, INR increased 1.26-fold. AUCs for R(+)-warfarin and S(-)-warfarin increased 25% and 30%, respectively. $C_{max}$ for R(+)-warfarin and S(-)-warfarin increased 14% and 15%, respectively. In patients taking coumarins (such as warfarin) and Lojuxta concomitantly, INR

should be determined before starting Lojuxta and monitored regularly with dosage of coumarins adjusted as clinically indicated (see section 4.4).

*Fenofibrate, niacin and ezetimibe*: When lomitapide was administered to steady state prior to micronised fenofibrate 145 mg, extended release niacin 1000 mg, or ezetimibe 10 mg, no clinically significant effects on the exposure of any of these medicinal products were observed. No dose adjustments are required when co-administered with Lojuxta.

*Oral contraceptives:* When lomitapide 50 mg was administered to steady state along with an oestrogen-based oral contraceptive, no clinically meaningful or statistically significant impact on the pharmacokinetics of the components of the oral contraceptive (ethinyl estradiol and 17-deacetyl norgestimate, the metabolite of norgestimate) was observed. Lomitapide is not expected to directly influence the efficacy of oestrogen based oral contraceptives; however diarrhoea and/or vomiting may reduce hormone absorption. In cases of protracted or severe diarrhoea and/or vomiting lasting more than 2 days, additional contraceptive measures should be used for 7 days after resolution of symptoms.

*P-gp substrates:* Lomitapide inhibits P-gp *in vitro*, and may increase the absorption of P-gp substrates. Coadministration of Lojuxta 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 Lojuxta.

*In vitro assessment of drug interactions*: Lomitapide inhibits CYP3A4. Lomitapide does not induce CYPs 1A2, 3A4, or 2B6, and does not inhibit CYPs 1A2, 2B6, 2C9, 2C19, 2D6, or 2E1. Lomitapide is not a P-gp substrate but does inhibit P-gp. Lomitapide does not inhibit breast cancer resistance protein (BCRP).

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Lojuxta is contraindicated during pregnancy. There are no reliable data on its use in pregnant women. Animal studies have shown developmental toxicity (teratogenicity, embryotoxicity, see section 5.3). The potential risk for humans is unknown.

Use in women of child-bearing potential

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. Patients taking oestrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting. Additional contraceptive measures should be used until resolution of symptoms (see section 4.5).

Breast-feeding

It is not known whether lomitapide is excreted into human milk. Because of the potential for adverse effects based on findings in animal studies with lomitapide (see section 5.3), a decision should be made whether to discontinue breast-feeding or discontinue the medicinal product, taking into account the importance of the medicinal product to the mother.

Fertility

No adverse effects on fertility were observed in male and female rats administered lomitapide at systemic exposures (AUC) estimated to be 4 to 5 times higher than in humans at the maximum recommended human dose (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Lojuxta may have a minor influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile

The most serious adverse reactions during treatment were liver aminotransferase abnormalities (see section 4.4).

The most common adverse reactions were gastrointestinal effects. Gastrointestinal adverse reactions were reported by 27 (93%) of 29 patients in the Phase 3 clinical trial. Diarrhoea 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. Gastrointestinal adverse reactions occurred more frequently during the dose escalation phase of the study and decreased once patients established the maximum tolerated dose of lomitapide.

Gastrointestinal adverse reactions of severe intensity were reported by 6 (21%) of 29 patients in the Phase 3 clinical trial, with the most common being diarrhoea (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.

The most commonly reported adverse reactions of severe intensity were diarrhoea (4 subjects, 14%), vomiting (3 patients, 10%), and abdominal distension and ALT increased (2 subjects each, 7%).

Tabulated list of adverse reactions

Frequency of the adverse reactions is defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 3 lists all adverse reactions reported across the 35 patients treated in the Phase 2 Study UP1001 and in the Phase 3 Study UP1002/AEGR-733-005 or its extension study AEGR-733-012.

**Table 3: Frequency of Adverse Reactions in HoFH Patients**

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| Infections and infestations | Common | Gastroenteritis |
| Metabolism and nutrition disorders | Very common | Decreased appetite |
| | Not known | Dehydration |
| Nervous system disorders | Common | Dizziness<br>Headache<br>Migraine |
| Gastrointestinal disorders | Very common | Diarrhoea<br>Nausea<br>Vomiting<br>Abdominal discomfort<br>Dyspepsia<br>Abdominal pain<br>Abdominal pain upper<br>Flatulence<br>Abdominal distension<br>Constipation |
| | Common | Gastritis<br>Rectal tenesmus<br>Aerophagia<br>Defaecation urgency<br>Eructation<br>Frequent bowel movements<br>Gastric dilatation<br>Gastric disorder<br>Gastrooesophageal reflux disease<br>Haemorrhoidal haemorrhage<br>Regurgitation |
| Hepatobiliary disorders | Common | Hepatic steatosis<br>Hepatotoxicity<br>Hepatomegaly |
| Skin and subcutaneous tissue disorders | Common | Ecchymosis<br>Papule<br>Rash erythematous<br>Xanthoma |
| | Not known | Alopecia |
| Musculoskeletal and connective tissue disorders | Not known | Myalgia |
| General disorders and administration site conditions | Common | Fatigue |
| Investigations | Very common | Alanine aminotransferase increased<br>Aspartate aminotransferase increased<br>Weight decreased |
| | Common | International normalised ratio increased<br>Blood alkaline phosphatase increased<br>Blood potassium decreased<br>Carotene decreased<br>International normalised ratio abnormal<br>Liver function test abnormal<br>Prothrombin time prolonged<br>Transaminases increased<br>Vitamin E decreased<br>Vitamin K decreased |

Table 4 lists all adverse reactions for subjects who received lomitapide monotherapy (N=291) treated in Phase 2 studies in subjects with elevated LDL-C (N=462).

**Table 4: Frequency of Adverse Reactions in Elevated LDL-C Patients**

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| Infections and infestations | Uncommon | Gastroenteritis<br>Gastrointestinal infection<br>Influenza<br>Nasopharyngitis<br>Sinusitis |
| Blood and lymphatic system disorders | Uncommon | Anaemia |
| Metabolism and nutrition disorders | Common | Decreased appetite |
| | Uncommon | Dehydration<br>Increased appetite |
| Nervous system disorders | Uncommon | Paraesthesia<br>Somnolence |
| Eye disorders | Uncommon | Eye swelling |
| Ear and labyrinth disorders | Uncommon | Vertigo |
| Respiratory, thoracic and mediastinal disorders | Uncommon | Pharyngeal lesion<br>Upper-airway cough syndrome |
| Gastrointestinal disorders | Very common | Diarrhoea<br>Nausea<br>Flatulence |
| | Common | Abdominal pain upper<br>Abdominal distension<br>Abdominal pain<br>Vomiting<br>Abdominal discomfort<br>Dyspepsia<br>Eructation<br>Abdominal pain lower<br>Frequent bowel movements |
| | Uncommon | Dry mouth<br>Faeces hard<br>Gastrooeosophageal reflux disease<br>Abdominal tenderness<br>Epigastric discomfort<br>Gastric dilatation<br>Haematemesis<br>Lower gastrointestinal haemorrhage<br>Reflux oesophagitis |
| Hepatobiliary disorders | Uncommon | Hepatomegaly |
| Skin and subcutaneous tissue disorders | Uncommon | Blister<br>Dry skin<br>Hyperhidrosis |
| Musculoskeletal and connective tissue disorders | Common | Muscle spasms |
| | Uncommon | Arthralgia<br>Myalgia<br>Pain in extremity<br>Joint swelling<br>Muscle twitching |
| Renal and urinary disorders | Uncommon | Haematuria |

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| General disorders and administrative site conditions | Common | Fatigue<br>Asthenia |
| | Uncommon | Chest pain<br>Chills<br>Early satiety<br>Gait disturbance<br>Malaise<br>Pyrexia |
| Investigations | Common | Alanine aminotransferase increased<br>Aspartate aminotransferase increased<br>Hepatic enzyme increased<br>Liver function test abnormal<br>Neutrophil count decreased<br>White blood cell count decreased |
| | Uncommon | Weight decreased<br>Blood bilirubin increased<br>Gamma-glutamyltransferase increased<br>Neutrophil percentage increased<br>Protein urine<br>Prothrombin time prolonged<br>Pulmonary function test abnormal<br>White blood cell count increased |

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

There is no specific treatment in the event of overdose. In rodents, single oral doses of lomitapide ≥600 times higher than the maximum recommended human dose (1 mg/kg) were well tolerated. The maximum dose administered to human subjects in clinical studies was 200 mg as a single dose; there were no adverse reactions.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other lipid modifying agents, plain. ATC code: C10AX12

Mechanism of action

Lomitapide is a selective inhibitor of microsomal 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 reduces lipoprotein secretion and circulating concentrations of lipoprotein-borne lipids including cholesterol and triglycerides.

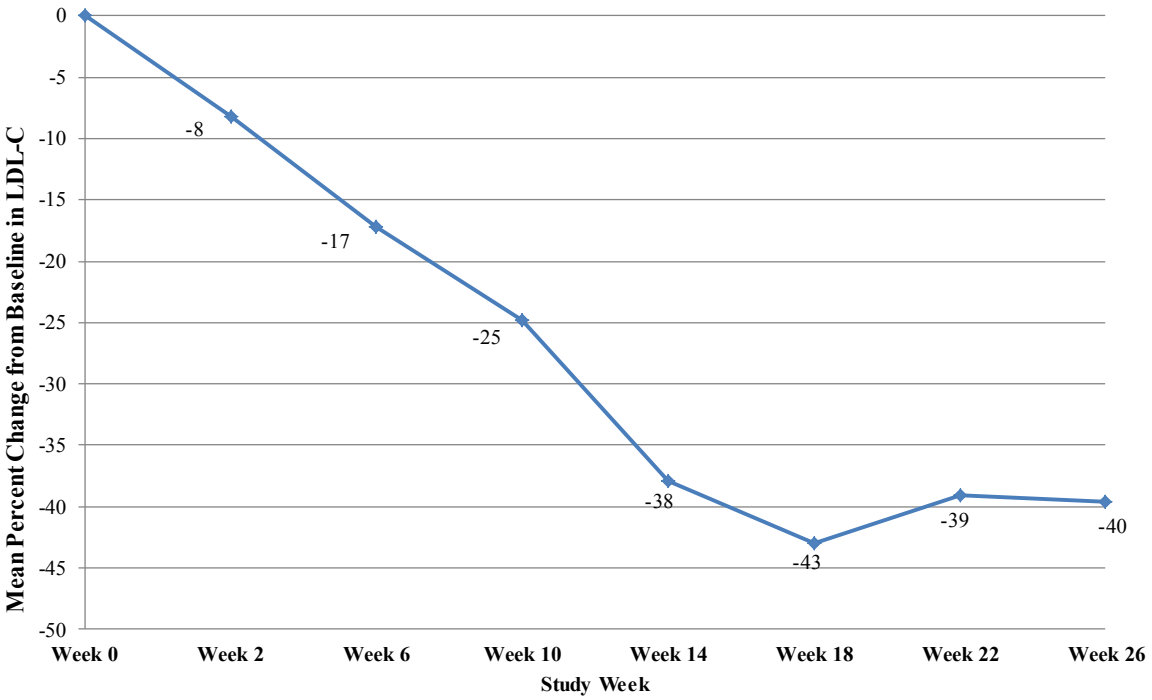
Clinical efficacy and safety

A single arm, open-label study (UP1002/AEGR-733-005) evaluated the efficacy and safety of lomitapide when co-administered with a low-fat diet and other lipid-lowering therapies in adult

patients with HoFH. Patients were instructed to maintain a low-fat diet (<20% calories from fat) and their lipid-lowering therapies at study entry, including apheresis if applicable, from 6 weeks prior to baseline through at least Week 26. The dose of lomitapide was escalated from 5 mg to an individually determined maximum tolerated dose up to 60 mg. After Week 26, patients remained on lomitapide to determine the effects of longer-term treatment and were allowed to change background lipid-lowering therapies. The study provided for a total of 78 weeks of treatment.

Twenty-nine patients were enrolled, of whom 23 completed through Week 78. Sixteen males (55%) and 13 females (45%) were included with a mean age of 30.7 years, ranging from 18 to 55 years. The mean dose of lomitapide was 45 mg at Week 26 and 40 mg at Week 78. At Week 26, the mean percent change in LDL-C from baseline of LDL-C was -40% ($p<0.001$) in the Intent to Treat (ITT) population. Mean percent change from baseline through Week 26 using last observation carried forward (LOCF) to each assessment is shown in Figure 1.

**Figure 1: Mean percent changes from baseline in LDL-C in the major effectiveness study UP1002/AEGR-733-005 through Week 26 (the Primary Endpoint) using LOCF to each assessment (N=29)**




Changes in lipids and lipoproteins through Week 26 and Week 78 of lomitapide treatment are presented in Table 5.

**Table 5: Absolute values and percent changes from baseline to Weeks 26 and 78 in lipids and lipoproteins (major effectiveness study UP1002/AEGR-733-005)**

| Parameter (units) | Baseline | Week 26/LOCF (N=29) | | | Week 78 (N=23) | | |
|---|---|---|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | % Change | p-value[b] | Mean (SD) | % Change | p-value[b] |
| LDL-C, direct (mg/dL) | 336 (114) | 190 (104) | -40 | <0.001 | 210 (132) | -38 | <0.001 |
| Total Cholesterol (TC) (mg/dL) | 430 (135) | 258 (118) | -36 | <0.001 | 281 (149) | -35 | <0.001 |
| Apolipoprotein B (apo B) (mg/dL) | 259 (80) | 148 (74) | -39 | <0.001 | 151 (89) | -43 | <0.001 |
| Triglycerides (TG) (mg/dL)[a] | 92 | 57 | -45 | 0.009 | 59 | -42 | 0.012 |
| Non high-density lipoprotein cholesterol (Non-HDL-C) (mg/dL) | 386 (132) | 217 (113) | -40 | <0.001 | 239 (146) | -39 | <0.001 |
| Very-low-density lipoprotein cholesterol (VLDL-C) (mg/dL) | 21 (10) | 13 (9) | -29 | 0.012 | 16 (15) | -31 | 0.013 |
| Lipoprotein (a) (Lp(a)) (nmol/L)[a] | 66 | 61 | -13 | 0.094 | 72 | -4 | <0.842 |
| High-density lipoprotein cholesterol (HDL-C) (mg/dL) | 44 (11) | 41 (13) | -7 | 0.072 | 43 (12) | -4.6 | 0.246 |

[a] Median presented for TG and Lp(a). p-value is based on the mean percent change
[b] p-value on the mean percent change from baseline based on paired t-test

At both Week 26 and Week 78, there were significant reductions in LDL-C, TC, apo B, TG, non-HDL-C, VLDL-C and changes in HDL-C trended lower at Week 26 and returned to baseline levels by Week 78.

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

At baseline, 93% were on a statin, 76% were on ezetimibe, 10% on niacin, 3% on a bile acid sequestrant and 62% were receiving apheresis. Fifteen of 23 (65%) patients had their lipid-lowering treatment reduced by Week 78, including planned and unplanned reductions/interruptions. Apheresis was discontinued in 3 out of 13 patients who were on it at Week 26, and frequency was reduced in 3 patients while maintaining low LDL-C levels through Week 78. The clinical benefit of reductions in background lipid-lowering therapy, including apheresis, is not certain.

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 and 1 having LDL-C <70 mg/dL at that time point.

In this study, 10 patients experienced elevations in AST and/or ALT >3 x ULN (see Table 6).

**Table 6: Highest liver function test results post first dose (major effectiveness study UP1002/AEGR-733-005)**

| Parameter/Abnormality | N (%) |
|---|---|
| ALT | |
| Number of Patients with Assessments | 29 |
| >3 to ≤5 x ULN | 6 (20.7) |
| >5 to ≤10 x ULN | 3 (10.3) |
| >10 to ≤20 x ULN | 1 (3.4) |
| >20 x ULN | 0 |
| AST | |
| Number of Patients with Assessments | 29 |
| >3 to ≤5 x ULN | 5 (17.2) |
| >5 to ≤10 x ULN | 1 (3.4) |
| >10 to ≤20 x ULN | 0 |
| >20 x ULN | 0 |

Elevations in ALT and/or AST >5 x ULN were managed with a dose reduction or temporary suspension of lomitapide dosing, and all patients were able to continue with study drug treatment. No clinically meaningful elevations in total bilirubin or alkaline phosphatase were observed. Hepatic fat was prospectively measured using MRS in all eligible patients during the clinical trial (Table 7). Data from individuals who had repeat measurements after stopping lomitapide show that hepatic fat accumulation is reversible, but whether histological sequelae remain is unknown.

**Table 7: Maximum categorical changes in % hepatic fat (major effectiveness study UP1002/AEGR-733-005)**

| 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) |

The European Medicines Agency has deferred the obligation to submit the results of studies with Lojuxta in one or more subsets of the paediatric population in HoFH (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption

The absolute oral bioavailability of lomitapide is 7%. Absorption is not limited by penetration of the drug across the intestinal barrier but is predominantly influenced by an extensive first pass effect. Peak plasma concentrations of lomitapide were reached 4-8 hours following oral dosing. Lomitapide pharmacokinetics is approximately dose-proportional for oral single doses in the therapeutic range. Doses higher than 60 mg suggest a trend toward nonlinearity and are not recommended.

Upon multiple dosing $C_{max}$ and AUC increased in approximate proportion to lomitapide dose. $C_{max}$ and AUC were increased following either a high-fat meal (77% and 58%, respectively) or low fat meal (70% and 28%, respectively). Accumulation of lomitapide in plasma was consistent with that predicted after a single dose following once daily oral dosing above 25 mg for up to 4 weeks. Inter-individual variability in lomitapide AUC was approximately 50%.

At steady state the accumulation of lomitapide was 2.7 at 25 mg and 3.9 at 50 mg.

Distribution

Following intravenous administration, the volume of distribution of lomitapide was high (mean=1200 litres) despite a high degree (>99.8%) of binding to plasma protein. In animal studies lomitapide was highly concentrated (200-fold) in the liver.

Biotransformation

Lomitapide is extensively metabolised, predominantly by CYP3A4. CYP isoforms 2E1, 1A2, 2B6, 2C8, and 2C19 are involved to a lesser extent and isoforms 2D6 and 2C9 are not involved in the metabolism of lomitapide.

Elimination

Following administration of a radiolabeled oral solution dose to healthy subjects, 93% of the administered dose was recovered in urine and faeces. Approximately 33% of the radioactivity was excreted in urine as metabolites. The remainder was excreted in faeces, primarily as oxidised metabolites. The elimination half-life of lomitapide was approximately 29 hours.

Special populations

Data in the pivotal clinical trial were analyzed with respect to the impact of potential covariates on lomitapide exposure. Of the parameters examined (race, body mass index (BMI), gender, weight, age), only BMI could be classified as a potential covariate.

*Age and gender*

There was no clinically relevant effect of age (18-64 years) or gender on the pharmacokinetics of lomitapide.

*Race*

No dose adjustment is required for Caucasian or Latino patients. There is insufficient information to determine if Lojuxta requires dose adjustment in other races. However, since the medicinal product is dosed in an escalating fashion according to individual patient safety and tolerability, no adjustment to the dosing regimen is recommended based on race.

*Renal insufficiency*

In the renal impairment population, lomitapide was only studied in patients with end-stage renal disease (ESRD). A pharmacokinetic study in patients with ESRD undergoing hemodialysis demonstrated a 36% increase in mean lomitapide plasma concentration compared to matched healthy controls. The terminal half-life of lomitapide was not affected.

*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. Lojuxta has not been studied in patients with severe hepatic impairment (Child-Pugh score 10-15).

*Paediatric population*

Lojuxta has not been investigated in children less than 18 years of age.

*Elderly population*

Lojuxta has not been investigated in patients aged 65 years or older.

## 5.3 Preclinical safety data

In repeat-dose oral toxicology studies in rodents and dogs, the principal drug-related findings were lipid accumulation in the small intestine and/or liver associated with decreases in serum cholesterol and/or triglyceride levels. These changes are secondary to the mechanism of action of lomitapide. Other liver-related changes in repeat-dose toxicity studies in rats and dogs included increased serum aminotransferases, subacute inflammation (rats only), and single-cell necrosis. In a 1 year repeat-dose study in dogs there were no microscopic changes in the liver although serum AST was minimally increased in females.

Pulmonary histiocytosis was observed in rodents. Decreased red blood cell parameters as well as poikilocytosis and/or anisocytosis were observed in dogs. Testicular toxicity was observed in dogs at 205 times the human exposure (AUC) at 60 mg in a 6-month study. No adverse effects on the testes were observed in a 1-year study in dogs at 64 times the human exposure at 60 mg.

In a dietary carcinogenicity study in mice, lomitapide was administered up to 104 weeks at doses ranging from 0.3 to 45 mg/kg/day. There were statistically significant increases in the incidences of liver adenoma and carcinoma at doses ≥1.5 mg/kg/day in males (≥ 2 times the human exposure at 60 mg daily based on AUC) and ≥7.5 mg/kg/day in females (≥ 9 times the human exposure at 60 mg based on AUC). Incidences of small intestinal carcinoma and/or combined adenoma and carcinoma (rare tumours in mice) were significantly increased at doses ≥15 mg/kg/day in males (≥ 26 times the human exposure at 60 mg based on AUC) and at 15 mg/kg/day in females (22 times the human exposure at 60 mg based on AUC).

In an oral carcinogenicity study in rats, lomitapide was administered up to 99 weeks at doses up to 7.5 mg/kg/day in males and 2.0 mg/kg/day in females. Focal hepatic fibrosis was observed in males and females and hepatic cystic degeneration was observed in males only. In high-dose males, an increased incidence of pancreatic acinar cell adenoma was observed at an exposure 6 times that in humans at 60 mg based on AUC.

Lomitapide was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* studies.

Lomitapide had no effect on reproductive function in female rats at doses up to 1 mg/kg or in male rats at doses up to 5 mg/kg. Systemic exposures to lomitapide at these doses were estimated to be 4 times (females) and 5 times (males) higher than the human exposure at 60 mg based on AUC.

Lomitapide was teratogenic in rats in the absence of maternal toxicity at an exposure (AUC) estimated to be twice that in humans at 60 mg. There was no evidence of embryofoetal toxicity in rabbits at 3 times the maximum recommended human dose (MRHD) of 60 mg based on body surface area. Embryofoetal toxicity was observed in rabbits in the absence of maternal toxicity at ≥6.5 times the MRHD. In ferrets, lomitapide was both maternally toxic and teratogenic at <1 times the MRHD.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule content
Pregelatinised starch (maize)
Sodium starch glycolate
Microcrystalline cellulose
Lactose monohydrate
Silica, colloidal anhydrous
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)

Printing ink
Shellac
Black iron oxide (E172)
Propylene glycol

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years.

### 6.4 Special precautions for storage

Store below 30°C.
Keep the bottle tightly closed in order to protect from moisture.

### 6.5 Nature and contents of container

High density polyethylene (HDPE) bottle fitted with a polyester/aluminium foil/cardboard induction seal and polypropylene screw cap.

Package sizes are:
28 capsules

### 6.6 Special precautions for disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Aegerion Pharmaceuticals Ltd
Lakeside House
1 Furzeground Way
Stockley Park East
Uxbridge UB11 1BD
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/851/006

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

**E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES**

## A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
Catalent UK Packaging Limited
Lancaster Way
Wingates Industrial Estate
Westhoughton
Bolton
Lancashire
BL5 3XX
United Kingdom

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal products on "restricted" medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall provide an educational pack prior to launch targeting all physicians who are expected to prescribe/use lomitapide.
The physician educational pack should contain:

- The Summary of Product Characteristics
- The Prescriber Guide
- Patient Alert Cards

- Patient Brochures

The MAH must agree the content and format of the educational materials together with a communication plan with the national competent authority in each Member State prior to distribution in their territory.

**The Prescriber Guide shall include the following key elements:**

Appropriate patient selection

- Lojuxta is only indicated for use in adult patients with HoFH;
- The safety and effectiveness of Lojuxta in children below the age of 18 have not been established;
- Treatment with Lojuxta should be initiated and monitored by a physician experienced in the treatment of lipid disorders;
- That Lojuxta was teratogenic in non-clinical studies and that women of child-bearing potential must be non-pregnant and using effective contraception prior to initiating treatment.

Gastrointestinal (GI) Effects

- Information on undesirable effects, including diarrhoea, nausea, flatulence, abdominal pain or discomfort, abdominal distension, vomiting, dyspepsia, eructation and decreased appetite;
- Contraindication for use in patients with a known significant or chronic bowel disease such as inflammatory bowel disease or malabsorption;
- Advice on escalating Lojuxta dose gradually to improve tolerability of the medicine;
- Advice to patients about:
  - The need to follow a low-fat diet (i.e. patients should follow a diet supplying less than 20% of energy from fat);
  - The timing of medicine intake (Lojuxta should be taken on an empty stomach, at least 2 hours after the evening meal);
  - The need to take daily dietary supplements (i.e. 400 IU vitamin E, approximately 200 mg linoleic acid, 110 mg eicosapentaenoic acid (EPA), 210 mg alpha linolenic acid (ALA) and 80 mg docosahexaenoic acid (DHA) per day).

Hepatic events related to elevated aminotransferases and progressive liver disease

- Information about contraindication in patients with moderate or severe pre-existing hepatic impairment/disease, including those with unexplained persistent abnormal liver function tests;
- Information about clinical findings (i.e., hepatic enzyme increases and steatosis) in subjects treated with Lojuxta during the developmental phase;
- Advice to exercise caution if Lojuxta is used with other hepatotoxic drugs and to consider more frequent monitoring of liver-related tests;
- Advice to patients about the risk of concomitant alcohol intake;
- Advice on monitoring liver function (measuring hepatic enzymes and total bilirubin) before and during treatment with Lojuxta and routine screening to detect presence of steatohepatitis and hepatic fibrosis including specific details of the screening tests at baseline and annually as follows:
  - Imaging for tissue elasticity, e.g. Fibroscan, acoustic radiation force impulse (ARFI), or magnetic resonance (MR) elastography;
  - Measurement of biomarkers and/or scoring methods. This should include at least one marker in each of the following categories:
    - gamma-GT, serum albumin (liver injury);
    - high sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), CK-18 Fragment, NashTest (liver inflammation);
    - Enhanced Liver Fibrosis (ELF) panel, Fibrometer, AST/ALT ratio, Fib-4 score, Fibrotest (liver fibrosis).

Use in Women of Childbearing Potential

- That Lomitapide was teratogenic in non-clinical studies and is contraindicated in women who are or may become pregnant. Women who become pregnant should be counselled and referred to an expert in teratology;
- Before initiating treatment in women of child-bearing potential:
  - The absence of pregnancy should be confirmed;
  - Appropriate advice on effective methods of contraception should be provided, and effective contraception initiated;
- Warning about possible loss of effectiveness of oral contraceptives due to diarrhoea or vomiting and need for additional contraception until 7 days after resolution of symptoms;
- Women should tell their doctor immediately if they suspect that they might be pregnant.

Drug interactions

- Information about interactions with CYP3A4 inhibitors and inducers, coumarin anticoagulants, statins, P-gp substrates, oral contraceptives, bile acid sequestrants and grapefruit juice;
- Importance of fatty acid and soluble vitamins supplementation;
- Compliance with the supplementation regimen should be verified at regular scheduled appointments and the importance emphasised.

**Educational materials for patients**

Information that the educational materials for patients included in the prescribers pack can be used for patient counselling.
A copy of the patient brochure and patient alert card shall be provided to all patients at the time Lojuxta treatment is initiated.
Patients shall be informed of the necessity to carry the patient alert card with them and show it to all doctors that treat them.
Lomitapide Observational Worldwide Evaluation Registry
Information about the existence and importance of the registry aiming to systematically collect information on the safety and effectiveness outcomes of patients treated with lomitapide.
Prescribers are encouraged to enrol all patients treated with Lojuxta into a global registry.

**Patient brochure**

The patient brochure shall include the following key elements:
- Not to take Lojuxta if patient has liver problems, or unexplained abnormal liver tests;
- Information that Lojuxta may cause liver problems;
- The need to inform their doctor if they have had any liver problems in the past;
- The need to inform their doctor of all other medications they are taking as special care should be taken if other drugs which can cause liver problems are taken at the same time;
- Symptoms of liver disease for which the patient should consult a doctor;
- An explanation of the types of tests required (imaging and blood) to check liver function and the importance of them being performed regularly;
- Information that Lojuxta was teratogenic in non-clinical studies and should not be taken during pregnancy or by patients trying to get pregnant;
- Women of childbearing potential should have adequate birth control and should tell their doctors immediately if they suspect they may be pregnant;
- Lojuxta may cause diarrhoea and vomiting and if it does, patients using oral contraception should use additional contraceptive methods for 7 days after symptoms have resolved;
- Information about interactions with CYP3A4 inhibitors and inducers, coumarin anticoagulants, statins, P-gp substrates, oral contraceptives, bile acid sequestrants;
- The need to avoid alcohol;
- The need to avoid grapefruit juice;
- Importance of fatty acid and fat soluble vitamin (Vitamin E) supplementation;

- Information on the importance of following a low-fat diet (a diet supplying less than 20% of energy from fat);
- Information about taking Lojuxta at bedtime with water at least 2 hours after the evening meal and without food;
- Information about the existence and importance of the Lomitapide Observational Worldwide Evaluation Registry aiming to systematically collect information on the safety and effectiveness outcomes of patients treated with lomitapide.

**Patient Alert card**

The purpose of the patient alert card is to inform health care professionals of potential drug-drug interactions before any additional drug is prescribed. Patients will be instructed to carry this card and show it to all doctors who treat them.

This card will give information about interactions with:

- CYP 3A4 inhibitors
- CYP 3A4 inducers
- coumarin anticoagulants
- statins
- P-gp substrates
- Oestrogen-containing oral contraceptives

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measure:

| **Description** | **Due date** |
|---|---|
| Based on CHMP approved protocol, the applicant shall conduct a clinical study with adequate surrogate endpoints on vascular outcomes using imaging techniques to monitor vascular function, disease stabilisation and/or regression. | The final study report shall be submitted by 31 December 2021. |

## E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

| Description | Due date |
|---|---|
| The applicant shall set up a long term prospective observational study to systematically collect information on the safety and effectiveness outcomes of patients treated with lomitapide.<br><br>The objectives of the study are:<br>• To evaluate the occurrence of the following in patients treated with lomitapide:<br>o Hepatic events<br>o Gastrointestinal events<br>o Small bowel, hepatic, colorectal and pancreatic tumours<br>o Events associated with coagulopathy<br>o Major Adverse Cardiovascular Events (MACE) events<br>o Death, including cause of death<br>• To evaluate the occurrence and outcomes of pregnancy in females of reproductive potential treated with lomitapide who decide to continue the pregnancy following advice from a teratologist.<br>• To evaluate the long-term effectiveness of lomitapide in maintaining control of serum lipid levels in clinical practice.<br>• To evaluate whether prescribers of lomitapide are following the screening and monitoring recommendations as specified in the product information and the educational materials. | Annual reports will be submitted at time of annual reassessment |

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**CARTON AND BOTTLE (5 mg, 10 mg, 20 mg, 30 mg, 40 mg and 60 mg)**

## 1. NAME OF THE MEDICINAL PRODUCT

Lojuxta 5 mg hard capsules
Lojuxta 10 mg hard capsules
Lojuxta 20 mg hard capsules
Lojuxta 30 mg hard capsules
Lojuxta 40 mg hard capsules
Lojuxta 60 mg hard capsules
lomitapide

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains lomitapide mesylate equivalent to 5 mg lomitapide.
Each hard capsule contains lomitapide mesylate equivalent to 10 mg lomitapide.
Each hard capsule contains lomitapide mesylate equivalent to 20 mg lomitapide.
Each hard capsule contains lomitapide mesylate equivalent to 30 mg lomitapide.
Each hard capsule contains lomitapide mesylate equivalent to 40 mg lomitapide.
Each hard capsule contains lomitapide mesylate equivalent to 60 mg lomitapide.

## 3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Keep the bottle tightly closed in order to protect from moisture.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aegerion Pharmaceuticals Ltd
Lakeside House
1 Furzeground Way
Stockley Park East
Uxbridge UB11 1BD
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/851/001
EU/1/13/851/002
EU/1/13/851/003
EU/1/13/851/004
EU/1/13/851/005
EU/1/13/851/006

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

lojuxta 5 mg
lojuxta 10 mg
lojuxta 20 mg
lojuxta 30 mg
lojuxta 40 mg
lojuxta 60 mg

# B. PACKAGE LEAFLET

**Package leaflet: information for the user**

**Lojuxta 5 mg hard capsules**
**Lojuxta 10 mg hard capsules**
**Lojuxta 20 mg hard capsules**
lomitapide

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Lojuxta is and what it is used for

Lojuxta contains the active substance called lomitapide. Lomitapide is a "lipid-modifying agent" which works by blocking the action of "microsomal triglyceride transfer protein." 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 (lipids) in the blood.

Lojuxta is used to treat adult patients with very high cholesterol because of a condition that runs in their families (homozygous familial hypercholesterolaemia or HoFH). It is typically passed down by both father and mother, who also have high cholesterol passed down from their parents. The patient's "bad" cholesterol level is very high from a very early age. The "bad" cholesterol can lead to heart attacks, strokes or other events at an early age. Lojuxta is used with a low-fat diet and other lipid lowering treatments to decrease your cholesterol levels.

Lojuxta can lower blood levels of:
- low density lipoprotein (LDL) cholesterol ("bad" cholesterol)
- total cholesterol
- apolipoprotein-B, a protein that carries "bad cholesterol" in the blood
- triglycerides (fat carried in the blood)

## 2. What you need to know before you take Lojuxta

**Do not take Lojuxta:**
- if you are allergic to lomitapide or any of the other ingredients of Lojuxta capsules (listed in section 6)
- if you have liver problems or unexplained abnormal liver tests
- if you have bowel problems or cannot absorb food from your bowel
- if you take more than 40 mg of simvastatin daily (another medicine used to lower cholesterol)
- if you take any of these medicines that affect the way lomitapide is broken down in the body:
    - itraconazole, ketoconazole, fluconazole, voriconazole, posaconazole (for fungal infections)
    - telithromycin, clarithromycin, erythromycin (for bacterial infections)
    - indinavir, nelfinavir, saquinavir (for HIV infection)
    - diltiazem, verapamil (for high blood pressure, or angina), and dronedarone (to regulate heart rhythm)
- if you are pregnant, trying to get pregnant, or think you may be pregnant (see section: 'Pregnancy and breast-feeding').

**Warnings and precautions**
Talk to your doctor or pharmacist before taking Lojuxta if you:

- have had liver problems, including liver problems whilst taking other medicines.
  These capsules may cause side effects which can also be symptoms of liver problems. These side-effects are listed in section 4 and you must **tell your doctor immediately** if you have any of these signs and symptoms, as they may be caused by liver damage. Your doctor will give you a blood test to check your liver before you start taking these capsules, if your dose is increased, and regularly during treatment. These blood tests help your doctor adjust your dose. If your tests show some liver problems, your doctor may decide to reduce your dose or stop the treatment.

You may in some cases experience loss of fluids/dehydration, e.g. in case of vomiting, nausea and diarrhoea. It is important to avoid dehydration by drinking enough fluids (see section 4, Possible side effects).

**Children and adolescents**
No studies have been conducted in children and adolescents under the age of 18. Therefore the use of this medicine in children and adolescents is not recommended.

**Other medicines and Lojuxta**
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

Other medicines may affect the way Lojuxta works. Do not take any of the following medicines with Lojuxta:
- some medicines for bacterial, fungal or HIV infection (see section: 'Do not take Lojuxta')
- some medicines for high blood pressure, angina or to regulate heart rhythm (see section: 'Do not take Lojuxta')

You must also tell your doctor or pharmacist if you are taking any of the following medicines, as they may need to change your dose of Lojuxta:
- medicines which lower cholesterol (e.g. atorvastatin)
- combined oral contraceptives (e.g. ethinylestradiol, norgestimate)
- glucocorticoids (e.g. beclometasone, prednisolone) steroid medicines used to treat inflammation in conditions such as severe asthma, arthritis
- medicines to treat cancer (e.g. bicalutamide, lapatinib, methotrexate, nilotinib, pazopanib, tamoxifen) or nausea/vomiting with cancer treatment (e.g. fosaprepitant)

- medicines to reduce the activity of the immune system (e.g. ciclosporin, tacrolimus)
- medicines to treat bacterial or fungal infections (e.g. nafcillin, azithromycin, roxithromycin, clotrimazole)
- medicines to treat and prevent blood clots (e.g. cilostazol, ticagrelor)
- medicines to treat angina – chest pain caused by the heart (e.g. ranolazine)
- medicines to reduce blood pressure (e.g. amlodipine, lacidipine)
- medicines to regulate heart rhythm (e.g. amiodarone)
- medicines to treat epilepsy (e.g. phenobarbital, carbamazepine, phenytoin)
- medicines to treat diabetes (e.g. pioglitazone, linagliptin)
- medicines to treat tuberculosis (e.g. isoniazid, rifampicin)
- tetracycline antibiotics to treat infections such as urinary tract infections
- medicines to treat anxiety disorders and depression (e.g. alprazolam, fluoxetine, fluvoxamine)
- antacids (e.g. ranitidine, cimetidine)
- aminoglutethimide – a medicine used to treat Cushing's syndrome
- medicines to treat severe acne (e.g. isotretinoin)
- paracetamol – to treat pain
- medicines to treat cystic fybrosis (e.g. ivacaftor)
- medicines to treat urinary incontinence (e.g. propiverine)
- medicines to treat low levels of sodium in the blood (e.g. tolvaptan)
- medicines to treat excessive daytime sleepiness (e.g. modafinil)
- some herbal medicines:
    - St. John's Wort (for depression)
    - Ginkgo (to improve memory)
    - Goldenseal (for inflammation and infection)

Lojuxta may affect the way other medicines work. Tell your doctor or pharmacist if you are taking any of the following medicines:

- oral contraceptives (see section 2: 'Pregnancy and breast-feeding')
- other medicines used to lower cholesterol such as:
    - statins such as simvastatin. The risk of liver damage is increased when this medicine is used at the same time as statins. Muscle aches and pains (myalgia) or weakness (myopathy) may also occur. **Contact your doctor immediately if you experience any unexplained muscle aches and pains, tenderness or weakness.** You should not take more than 40 mg of simvastatin when using Lojuxta (see section 'Do not take Lojuxta')
- coumarin anticoagulants for thinning the blood ( e.g. warfarin)
- medicines to treat cancer (e.g. everolimus, imatinib, lapatinib, nilotinib, topotecan)
- medicines to reduce the activity of the immune system (e.g. sirolimus)
- medicines to treat HIV (e.g. maraviroc)
- medicines to treat and prevent blood clots (e.g. dabigatran etexilate)
- medicines to treat angina – chest pain caused by the heart (e.g. ranolazine)
- medicines to reduce blood pressure (e.g. talinolol, aliskiren, ambrisentan)
- medicines to regulate heart rhythm (e.g. digoxin)
- medicines to treat diabetes (e.g. saxagliptin, sitagliptin)
- medicines to treat gout (e.g. colchicine)
- medicines to treat low blood sodium level (e.g. tolvaptan)
- anti-histamine medicines to treat hayfever (e.g. fexofenadine)

**Lojuxta with food, drink and alcohol**

- Do not drink grapefruit juice.
- The use of alcohol during Lojuxta treatment is not recommended.
- Your dose of Lojuxta may need to be adjusted if you consume peppermint oil or Seville oranges.
- To lower the chance of stomach problems, you must stay on a low-fat diet whilst taking this medicine. Work with a dietitian to learn what you can eat while taking Lojuxta.

**Pregnancy and breast-feeding**
Do not take this medicine if you are pregnant, trying to get pregnant, or think you may be pregnant, as there is a possibility that it could harm an unborn baby. If you get pregnant while taking this medicine, call your doctor immediately and stop taking the capsules.

Pregnancy
- Before starting treatment you should confirm you are not pregnant and are using effective contraception, as advised by your doctor. If you use contraceptive pills and suffer from an episode of diarrhoea or vomiting that lasts more than 2 days, you must use an alternative method of contraception (e.g. condoms, diaphragm) for 7 days following resolution of symptoms.
- If, after you have started treatment with Lojuxta, you decide that you would like to become pregnant, please inform your doctor, as your treatment will need to be changed.

Breast-feeding
- It is not known if Lojuxta is passed into breast milk. Please tell your doctor if you are breast-feeding or planning to breast-feed. Your doctor may advise you to stop taking Lojuxta or to stop breast-feeding.

**Driving and using machines**
Your treatment may affect your ability to drive or operate machines. If you feel dizzy during treatment then do not drive or operate machines until you feel better.

**Lojuxta contains lactose.**
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

## 3. How to take Lojuxta

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. These capsules should be given to you by a doctor experienced in the treatment of lipid disorders who will also monitor you regularly.

The recommended starting dose is a 5 mg capsule each day. Your doctor may increase your dose slowly over time, up to a maximum of 60 mg each day. Your doctor will tell you:
- what dose to take and for how long.
- when to increase or decrease your dose.

Do not change the dose yourself.

- Take this medicine once a day at bedtime with water at least 2 hours after your evening meal (see section 2: 'Lojuxta with food, drink and alcohol').
- Do not take this medicine with food, as taking these capsules with food can cause stomach problems.
- If you take another medicine that lowers cholesterol by binding bile acids, such as colesevelam or cholestyramine, take the medicine that binds bile acids at least **4 hours before or 4 hours after** you take Lojuxta.

Because of the possibility of interactions with other medications, your doctor may change the time of day you take your medications. Alternatively, your doctor may decrease your dose of Lojuxta. Inform your doctor of any change in the medications you are taking.

You also need to take daily vitamin E and essential fatty acid (omega-3 and omega-6) supplements while taking this medicine. The usual dose that you will need to take is listed below. Ask your doctor, or dietitian how to obtain these supplements. See section 2: Lojuxta with food, drink and alcohol.

| **Daily Amount** | |
|---|---|
| **Vitamin E** | 400 IU* |
| **Omega-3** | **Approximately** |
| EPA | 110 mg* |
| DHA | 80 mg |
| ALA | 210 mg |
| **Omega-6** | |
| Linoleic acid | 200 mg |

* IU – international units, mg - milligrams

**If you take more Lojuxta than you should**
Contact your doctor or pharmacist immediately.

**If you forget to take Lojuxta**
Just take your normal dose at the usual time the next day. Do not take a double dose to make up for a forgotten dose.

**If you stop taking Lojuxta**
If you stop taking this medicine your cholesterol may rise again. You should contact your doctor before you stop taking this medicine.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Serious side effects:**

- abnormal blood tests for liver function have been reported commonly (may affect up to 1 in 10 people). The signs and symptoms of liver problems include:
  - nausea (feeling sick)
  - vomiting (being sick)
  - stomach pain
  - muscle aches and pains
  - fever
  - skin or whites of your eyes turn yellow
  - being more tired than usual
  - feeling like you have the flu

**Tell your doctor immediately** if you have any of these symptoms as your doctor may decide to stop the treatment.

The following other side effects have also occurred:

**Very common (may affect more than 1 in 10 people):**

- diarrhoea
- nausea and vomiting (feeling or being sick)
- stomach pain, discomfort or stomach bloating
- decreased appetite
- indigestion
- flatulence (wind)
- constipation
- weight loss

**Common (may affect up to 1 in 10 people):**
- inflammation of the stomach and intestine that causes diarrhoea and vomiting
- regurgitation (bringing food back up)
- burping
- feeling of incomplete defaecation (bowel movement), urgent need to defaecate
- bleeding from your rectum (back passage) or blood in your stool
- dizziness, headache, migraine
- tiredness, lack of energy or general weakness
- enlarged, damaged or fatty liver
- purple discoloration of the skin, solid bumps on the skin, rash, yellow bumps on the skin
- changes to blood clotting tests
- changes to blood cell count
- decrease in levels of potassium, carotene, vitamin E, vitamin K in your blood
- muscle spasms

**Uncommon (may affect up to 1 in 100 people):**
- flu or cold, fever, inflammation of your sinuses, cough
- low red blood cell count (anaemia)
- dehydration, dry mouth
- increased appetite
- burning or prickling of the skin
- swelling of the eye
- ulcer or sore spot in the throat
- vomiting blood
- dry skin
- blister
- excessive sweating
- joint pain or swelling, pain in hands or feet
- muscle pain
- blood or protein in the urine
- chest pain
- changes to your walking (gait)
- abnormal lung function test

**Not known (frequency cannot be estimated from the available data)**
- hair loss (alopecia)
- muscle pain (myalgia)
- loss of fluid that may cause headache, dry mouth, dizziness, tiredness or unconsciousness (dehydration)

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Lojuxta

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label or carton after “EXP”. The expiry date refers to the last day of that month.

Store below 30°C.
Keep the bottle tightly closed in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

## 6. Contents of the pack and other information

**What Lojuxta contains**

- The active substance is lomitapide.
  Lojuxta 5 mg: each hard capsule contains lomitapide mesylate equivalent to 5 mg lomitapide.
  Lojuxta 10 mg: each hard capsule contains lomitapide mesylate equivalent to 10 mg lomitapide.
  Lojuxta 20 mg: each hard capsule contains lomitapide mesylate equivalent to 20 mg lomitapide.
- The other ingredients are: pregelatinized starch, sodium starch glycolate, microcrystalline cellulose, lactose monohydrate, silica colloidal anhydrous and magnesium stearate (for information on lactose monohydrate, see section 2: Lojuxta contains lactose).

Capsule shell:

- The capsule shell for the 5 mg and 10 mg capsules contains gelatin, titanium dioxide (E171) and red iron oxide (E172).
- The capsule shell for the 20 mg capsule contains gelatin and titanium dioxide (E171).
- All capsules have edible black ink for printing.

**What Lojuxta looks like and contents of the pack**

- Lojuxta 5 mg is an orange cap/orange body hard capsule with “5 mg” printed on the body and “A733“ printed on the cap in black ink.
- Lojuxta 10 mg is an orange cap/white body hard capsule with “10 mg” printed on the body and “A733“ printed on the cap in black ink.
- Lojuxta 20 mg is a white cap/white body hard capsule with “20 mg” printed on the body and “A733” printed on the cap in black ink.

Pack sizes are:
- 28 capsules of Lojuxta 5 mg
- 28 capsules of Lojuxta 10 mg
- 28 capsules of Lojuxta 20 mg

**Marketing Authorisation Holder**
Aegerion Pharmaceuticals Ltd
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**Manufacturer**
Catalent UK Packaging Limited
Lancaster Way, Wingates Industrial Estate, Westhoughton, Bolton, Lancashire, BL5 3XX
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last revised in <{MM/YYYY}> <{month YYYY}.>**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

**Package leaflet: information for the user**

**Lojuxta 30 mg hard capsules**
**Lojuxta 40 mg hard capsules**
**Lojuxta 60 mg hard capsules**
lomitapide

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Lojuxta is and what it is used for

Lojuxta contains the active substance called lomitapide. Lomitapide is a "lipid-modifying agent" which works by blocking the action of "microsomal triglyceride transfer protein." 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 (lipids) in the blood.

Lojuxta is used to treat adult patients with very high cholesterol because of a condition that runs in their families (homozygous familial hypercholesterolaemia or HoFH). It is typically passed down by both father and mother, who also have high cholesterol passed down from their parents. The patient's "bad" cholesterol level is very high from a very early age. The "bad" cholesterol can lead to heart attacks, strokes or other events at an early age. Lojuxta is used with a low-fat diet and other lipid lowering treatments to decrease your cholesterol levels.

Lojuxta can lower blood levels of:
- low density lipoprotein (LDL) cholesterol ("bad" cholesterol)
- total cholesterol
- apolipoprotein-B, a protein that carries "bad cholesterol" in the blood
- triglycerides (fat carried in the blood)

## 2. What you need to know before you take Lojuxta

**Do not take Lojuxta:**
- if you are allergic to lomitapide or any of the other ingredients of Lojuxta capsules (listed in section 6)
- if you have liver problems or unexplained abnormal liver tests
- if you have bowel problems or cannot absorb food from your bowel
- if you take more than 40 mg of simvastatin daily (another medicine used to lower cholesterol)
- if you take any of these medicines that affect the way lomitapide is broken down in the body:
    - itraconazole, ketoconazole, fluconazole, voriconazole, posaconazole (for fungal infections)
    - telithromycin, clarithromycin, erythromycin (for bacterial infections)
    - indinavir, nelfinavir, saquinavir (for HIV infection)
    - diltiazem, verapamil (for high blood pressure, or angina), and dronedarone (to regulate heart rhythm)
- if you are pregnant, trying to get pregnant, or think you may be pregnant (see section: 'Pregnancy and breast-feeding').

**Warnings and precautions**
Talk to your doctor or pharmacist before taking Lojuxta if you:

- have had liver problems, including liver problems whilst taking other medicines.
  These capsules may cause side effects which can also be symptoms of liver problems. These side-effects are listed in section 4 and you must **tell your doctor immediately** if you have any of these signs and symptoms, as they may be caused by liver damage. Your doctor will give you a blood test to check your liver before you start taking these capsules, if your dose is increased, and regularly during treatment. These blood tests help your doctor adjust your dose. If your tests show some liver problems, your doctor may decide to reduce your dose or stop the treatment.

You may in some cases experience loss of fluids/dehydration, e.g. in case of vomiting, nausea and diarrhoea. It is important to avoid dehydration by drinking enough fluids (see section 4, Possible side effects).

**Children and adolescents**
No studies have been conducted in children and adolescents under the age of 18. Therefore the use of this medicine in children and adolescents is not recommended.

**Other medicines and Lojuxta**
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

Other medicines may affect the way Lojuxta works. Do not take any of the following medicines with Lojuxta:
- some medicines for bacterial, fungal or HIV infection (see section: 'Do not take Lojuxta')
- some medicines for high blood pressure, angina or to regulate heart rhythm (see section: 'Do not take Lojuxta')

You must also tell your doctor or pharmacist if you are taking any of the following medicines, as they may need to change your dose of Lojuxta:
- medicines which lower cholesterol (e.g. atorvastatin)
- combined oral contraceptives (e.g. ethinylestradiol, norgestimate)
- glucocorticoids (e.g. beclometasone, prednisolone) steroid medicines used to treat inflammation in conditions such as severe asthma, arthritis
- medicines to treat cancer (e.g. bicalutamide, lapatinib, methotrexate, nilotinib, pazopanib, tamoxifen) or nausea/vomiting with cancer treatment (e.g. fosaprepitant)

- medicines to reduce the activity of the immune system (e.g. ciclosporin, tacrolimus)
- medicines to treat bacterial or fungal infections (e.g. nafcillin, azithromycin, roxithromycin, clotrimazole)
- medicines to treat and prevent blood clots (e.g. cilostazol, ticagrelor)
- medicines to treat angina – chest pain caused by the heart (e.g. ranolazine)
- medicines to reduce blood pressure (e.g. amlodipine, lacidipine)
- medicines to regulate heart rhythm (e.g. amiodarone)
- medicines to treat epilepsy (e.g. phenobarbital, carbamazepine, phenytoin)
- medicines to treat diabetes (e.g. pioglitazone, linagliptin)
- medicines to treat tuberculosis (e.g. isoniazid, rifampicin)
- tetracycline antibiotics to treat infections such as urinary tract infections
- medicines to treat anxiety disorders and depression (e.g. alprazolam, fluoxetine, fluvoxamine)
- antacids (e.g. ranitidine, cimetidine)
- aminoglutethimide – a medicine used to treat Cushing's syndrome
- medicines to treat severe acne (e.g. isotretinoin)
- paracetamol – to treat pain
- medicines to treat cystic fybrosis (e.g. ivacaftor)
- medicines to treat urinary incontinence (e.g. propiverine)
- medicines to treat low levels of sodium in the blood (e.g. tolvaptan)
- medicines to treat excessive daytime sleepiness (e.g. modafinil)
- some herbal medicines:
    - St. John's Wort (for depression)
    - Ginkgo (to improve memory)
    - Goldenseal (for inflammation and infection)

Lojuxta may affect the way other medicines work. Tell your doctor or pharmacist if you are taking any of the following medicines:

- oral contraceptives (see section 2: 'Pregnancy and breast-feeding')
- other medicines used to lower cholesterol such as:
    - statins such as simvastatin. The risk of liver damage is increased when this medicine is used at the same time as statins. Muscle aches and pains (myalgia) or weakness (myopathy) may also occur. **Contact your doctor immediately if you experience any unexplained muscle aches and pains, tenderness or weakness.** You should not take more than 40 mg of simvastatin when using Lojuxta (see section 'Do not take Lojuxta')
- coumarin anticoagulants for thinning the blood ( e.g. warfarin)
- medicines to treat cancer (e.g. everolimus, imatinib, lapatinib, nilotinib, topotecan)
- medicines to reduce the activity of the immune system (e.g. sirolimus)
- medicines to treat HIV (e.g. maraviroc)
- medicines to treat and prevent blood clots (e.g. dabigatran etexilate)
- medicines to treat angina – chest pain caused by the heart (e.g. ranolazine)
- medicines to reduce blood pressure (e.g. talinolol, aliskiren, ambrisentan)
- medicines to regulate heart rhythm (e.g. digoxin)
- medicines to treat diabetes (e.g. saxagliptin, sitagliptin)
- medicines to treat gout (e.g. colchicine)
- medicines to treat low blood sodium level (e.g. tolvaptan)
- anti-histamine medicines to treat hayfever (e.g. fexofenadine)

**Lojuxta with food, drink and alcohol**

- Do not drink grapefruit juice.
- The use of alcohol during Lojuxta treatment is not recommended.
- Your dose of Lojuxta may need to be adjusted if you consume peppermint oil or Seville oranges.
- To lower the chance of stomach problems, you must stay on a low-fat diet whilst taking this medicine. Work with a dietitian to learn what you can eat while taking Lojuxta.

**Pregnancy and breast-feeding**
Do not take this medicine if you are pregnant, trying to get pregnant, or think you may be pregnant, as there is a possibility that it could harm an unborn baby. If you get pregnant while taking this medicine, call your doctor immediately and stop taking the capsules.

Pregnancy
- Before starting treatment you should confirm you are not pregnant and are using effective contraception, as advised by your doctor. If you use contraceptive pills and suffer from an episode of diarrhoea or vomiting that lasts more than 2 days, you must use an alternative method of contraception (e.g. condoms, diaphragm) for 7 days following resolution of symptoms.
- If, after you have started treatment with Lojuxta, you decide that you would like to become pregnant, please inform your doctor, as your treatment will need to be changed.

Breast-feeding
- It is not known if Lojuxta is passed into breast milk. Please tell your doctor if you are breast-feeding or planning to breast-feed. Your doctor may advise you to stop taking Lojuxta or to stop breast-feeding.

**Driving and using machines**
Your treatment may affect your ability to drive or operate machines. If you feel dizzy during treatment then do not drive or operate machines until you feel better.

**Lojuxta contains lactose.**
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

## 3. How to take Lojuxta

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. These capsules should be given to you by a doctor experienced in the treatment of lipid disorders who will also monitor you regularly.

The recommended starting dose is a 5 mg capsule each day. Your doctor may increase your dose slowly over time, up to a maximum of 60 mg each day. Your doctor will tell you:
- what dose to take and for how long.
- when to increase or decrease your dose.

Do not change the dose yourself.

- Take this medicine once a day at bedtime with water at least 2 hours after your evening meal (see section 2: 'Lojuxta with food, drink and alcohol').
- Do not take this medicine with food, as taking these capsules with food can cause stomach problems.
- If you take another medicine that lowers cholesterol by binding bile acids, such as colesevelam or cholestyramine, take the medicine that binds bile acids at least **4 hours before or 4 hours after** you take Lojuxta.

Because of the possibility of interactions with other medications, your doctor may change the time of day you take your medications. Alternatively, your doctor may decrease your dose of Lojuxta. Inform your doctor of any change in the medications you are taking.

You also need to take daily vitamin E and essential fatty acid (omega-3 and omega-6) supplements while taking this medicine. The usual dose that you will need to take is listed below. Ask your doctor, or dietitian how to obtain these supplements. See section 2: Lojuxta with food, drink and alcohol.

| **Daily Amount** | |
|---|---|
| **Vitamin E** | 400 IU* |
| **Omega-3** | **Approximately** |
| EPA | 110 mg* |
| DHA | 80 mg |
| ALA | 210 mg |
| **Omega-6** | |
| Linoleic acid | 200 mg |

* IU – international units, mg - milligrams

**If you take more Lojuxta than you should**
Contact your doctor or pharmacist immediately.

**If you forget to take Lojuxta**
Just take your normal dose at the usual time the next day. Do not take a double dose to make up for a forgotten dose.

**If you stop taking Lojuxta**
If you stop taking this medicine your cholesterol may rise again. You should contact your doctor before you stop taking this medicine.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Serious side effects:**

- abnormal blood tests for liver function have been reported commonly (may affect up to 1 in 10 people). The signs and symptoms of liver problems include:
  - nausea (feeling sick)
  - vomiting (being sick)
  - stomach pain
  - muscle aches and pains
  - fever
  - skin or whites of your eyes turn yellow
  - being more tired than usual
  - feeling like you have the flu

**Tell your doctor immediately** if you have any of these symptoms as your doctor may decide to stop the treatment.

The following other side effects have also occurred:

**Very common (may affect more than 1 in 10 people):**

- diarrhoea
- nausea and vomiting (feeling or being sick)
- stomach pain, discomfort or stomach bloating
- decreased appetite
- indigestion
- flatulence (wind)
- constipation
- weight loss

**Common (may affect up to 1 in 10 people):**
- inflammation of the stomach and intestine that causes diarrhoea and vomiting
- regurgitation (bringing food back up)
- burping
- feeling of incomplete defaecation (bowel movement), urgent need to defaecate
- bleeding from your rectum (back passage) or blood in your stool
- dizziness, headache, migraine
- tiredness, lack of energy or general weakness
- enlarged, damaged or fatty liver
- purple discoloration of the skin, solid bumps on the skin, rash, yellow bumps on the skin
- changes to blood clotting tests
- changes to blood cell count
- decrease in levels of potassium, carotene, vitamin E, vitamin K in your blood
- muscle spasms

**Uncommon (may affect up to 1 in 100 people):**
- flu or cold, fever, inflammation of your sinuses, cough
- low red blood cell count (anaemia)
- dehydration, dry mouth
- increased appetite
- burning or prickling of the skin
- swelling of the eye
- ulcer or sore spot in the throat
- vomiting blood
- dry skin
- blister
- excessive sweating
- joint pain or swelling, pain in hands or feet
- muscle pain
- blood or protein in the urine
- chest pain
- changes to your walking (gait)
- abnormal lung function test

**Not known (frequency cannot be estimated from the available data)**
- hair loss (alopecia)
- muscle pain (myalgia)
- loss of fluid that may cause headache, dry mouth, dizziness, tiredness or unconsciousness (dehydration)

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Lojuxta

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label or carton after "EXP". The expiry date refers to the last day of that month.

Store below 30°C.
Keep the bottle tightly closed in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

## 6. Contents of the pack and other information

**What Lojuxta contains**

- The active substance is lomitapide.
  Lojuxta 30 mg: each hard capsule contains lomitapide mesylate equivalent to 30 mg lomitapide.
  Lojuxta 40 mg: each hard capsule contains lomitapide mesylate equivalent to 40 mg lomitapide.
  Lojuxta 60 mg: each hard capsule contains lomitapide mesylate equivalent to 60 mg lomitapide.
- The other ingredients are: pregelatinized starch, sodium starch glycolate, microcrystalline cellulose, lactose monohydrate, silica colloidal anhydrous and magnesium stearate (for information on lactose monohydrate, see section 2: Lojuxta contains lactose).

Capsule shell:

- The capsule shell for the 30 mg capsule contains gelatin, titanium dioxide (E171), red iron oxide (E172) and yellow iron oxide (E172).
- The capsule shell for the 40 mg capsule contains gelatin, titanium dioxide (E171) and yellow iron oxide (E172).
- The capsule shell for the 60 mg capsule contains gelatin, titanium dioxide (E171) and yellow iron oxide (E172).
- All capsules have edible black ink for printing.

**What Lojuxta looks like and contents of the pack**

- Lojuxta 30 mg is an orange cap/yellow body hard capsule with “30 mg” printed on the body and “A733” printed on the cap in black ink.
- Lojuxta 40 mg is a yellow cap/white body hard capsule with “40 mg” printed on the body and “A733” printed on the cap in black ink.
- Lojuxta 60 mg is a yellow cap/yellow body hard capsule with “60 mg” printed on the body and “A733” printed on the cap in black ink.

Pack sizes are:
- 28 capsules of Lojuxta 30 mg
- 28 capsules of Lojuxta 40 mg
- 28 capsules of Lojuxta 60 mg

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**Manufacturer**
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.