SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lojuxta 5 mg
Lojuxta 10 mg
Lojuxta 20 mg

Hard Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lojuxta 5 mg hard capsules
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).

Lojuxta 10 mg hard capsules
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).

Lojuxta 20 mg hard capsules
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.

Patient safety information card
The marketing of Lojuxta is subject to a Risk management plan (RMP) including a 'patient safety information card'. The 'patient safety information card', emphasizes important safety information that the patient should be aware of before and during the treatment. Please explain to the patient the need to review the card before starting treatment.

3. PHARMACEUTICAL FORM

Hard, capsule.

Lojuxta 5 mg hard capsules
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.

Lojuxta 10 mg hard capsules
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.

Lojuxta 20 mg hard capsules
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 treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolaemia (HoFH).

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, according to LDL-C response and 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 4.4).

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

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 treatment, and should continue this diet during treatment. Dietary counselling should be provided.

Patients should avoid consumption of grapefruit juice and alcohol (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 medicinal products 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 cytochrome P450 (CYP) 3A4 inhibitor, separate the dose of the medicinal products (Lojuxta and the weak CYP3A4 inhibitor) by 12 hours. Exercise additional caution if administering more than 1 weak CYP3A4 inhibitor with Lojuxta. Consider limiting the maximum dose of Lojuxta according to desired LDL-C response.

Based on observations of decreased essential fatty acid and vitamin E levels in clinical studies, 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 (see section 4.4).

Special populations

Elderly population
There is limited experience with lomitapide 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
Lomitapide is contraindicated in patients with moderate or severe hepatic impairment including patients with unexplained persistent abnormal liver function tests (see sections 4.3 and 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 lomitapide 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.

Administration with food may increase exposure to lomitapide. It 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 (see section 4.4).

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 (see section 4.2).
- 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 CYP3A4 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

Lomitapide can cause elevations in the liver enzymes alanine aminotransferase [ALT] and aspartate aminotransferase [AST] and hepatic steatosis (see section 5.1). There have been no concomitant or subsequent clinically meaningful elevations in serum bilirubin, International Normalised Ratio (INR), or alkaline phosphatase. The extent to which lomitapide-associated hepatic steatosis promotes the elevations in aminotransferase is unknown. The liver enzyme changes can occur at any time during therapy, but occur most often during dose escalation.
Although cases of hepatic dysfunction (elevated aminotransferase with increase in bilirubin or 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.

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).

Dose modification based on elevated hepatic aminotransferases

Table 1 summarises 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. • If confirmed, reduce the dose and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR). • Repeat tests weekly and withhold dosing if there are signs of abnormal liver function (increase in bilirubin or INR), if aminotransferase levels rise above 5 x 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. • 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. • 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 lomitapide 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 adverse reactions 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 studies, 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

Medicinal products 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 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, 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 lomitapide 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 study for one of five patients taking concomitant warfarin. Patients taking warfarin should undergo regular monitoring of the INR, especially after any changes in the dose of Lojuxta. 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 study, 3 of 4 patients with ALT elevations >5x ULN reported alcohol consumption beyond the limits recommended in the protocol. The use of alcohol during lomitapide 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 lomitapide 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 study, patients were provided daily dietary supplements of vitamin E, linoleic acid, ALA, EPA and DHA. In this study, 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).

Excipients with known effect

Lactose

Lojuxta contains lactose. Patients with rare hereditary problems of galactose intolerance, total-lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on lomitapide 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	Strong and moderate inhibitors 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. Interactions between moderate CYP3A4 inhibitors and lomitapide have not been studied. 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.	Strong and moderate inhibitors 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). 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.

Medicinal products	**Effects on lomitapide levels**	**Recommendation concerning co-administration with Lojuxta**

	<u>Weak inhibitors</u> Weak CYP3A4 inhibitors are expected to increase the exposure of lomitapide when taken simultaneously. 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, no clinically meaningful increase in lomitapide exposure was observed. 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.	<u>Weak inhibitors</u> 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 list is not intended to be comprehensive and prescribers should check the prescribing information of medicinal products to be co-administered with Lojuxta for potential CYP3A4 mediated interactions. 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. 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

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).

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.

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 has 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 study. 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 study, 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 study 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

The adverse reactions are listed below by SOC (System Organ Class) and by frequency, most frequent reactions first. 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 Headache Migraine
Gastrointestinal disorders	Very common	Diarrhoea Nausea Vomiting Abdominal discomfort Dyspepsia Abdominal pain Abdominal pain upper Flatulence Abdominal distension Constipation
	Common	Gastritis Rectal tenesmus Aerophagia Defaecation urgency Eructation Frequent bowel movements Gastric dilatation Gastric disorder Gastro-oesophageal reflux disease Haemorrhoidal haemorrhage Regurgitation
Hepatobiliary disorders	Common	Hepatic steatosis Hepatotoxicity Hepatomegaly
Skin and subcutaneous tissue disorders	Common	Ecchymosis Papule Rash erythematous 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 Aspartate aminotransferase increased Weight decreased
	Common	International normalised ratio increased Blood alkaline phosphatase increased Blood potassium decreased Carotene decreased International normalised ratio abnormal Liver function test abnormal Prothrombin time prolonged Transaminases increased Vitamin E decreased 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 Gastrointestinal infection Influenza Nasopharyngitis Sinusitis
Blood and lymphatic system disorders	Uncommon	Anaemia
Metabolism and nutrition disorders	Common	Decreased appetite
	Uncommon	Dehydration Increased appetite
Nervous system disorders	Uncommon	Paraesthesia Somnolence
Eye disorders	Uncommon	Eye swelling
Ear and labyrinth disorders	Uncommon	Vertigo
Respiratory, thoracic and mediastinal disorders	Uncommon	Pharyngeal lesion Upper-airway cough syndrome
Gastrointestinal disorders	Very common	Diarrhoea Nausea Flatulence
	Common	Abdominal pain upper Abdominal distension Abdominal pain Vomiting Abdominal discomfort Dyspepsia Eructation Abdominal pain lower Frequent bowel movements
	Uncommon	Dry mouth Faeces hard Gastro-oeosophageal reflux disease Abdominal tenderness Epigastric discomfort Gastric dilatation Haematemesis Lower gastrointestinal haemorrhage Reflux oesophagitis
Hepatobiliary disorders	Uncommon	Hepatomegaly
Skin and subcutaneous tissue disorders	Uncommon	Blister Dry skin Hyperhidrosis
Musculoskeletal and connective tissue disorders	Common	Muscle spasms
	Uncommon	Arthralgia Myalgia Pain in extremity Joint swelling Muscle twitching
Renal and urinary disorders	Uncommon	Haematuria

System Organ Class	Frequency	Adverse reaction
General disorders and administrative site conditions	Common	Fatigue Asthenia
	Uncommon	Chest pain Chills Early satiety Gait disturbance Malaise Pyrexia
Investigations	Common	Alanine aminotransferase increased Aspartate aminotransferase increased Hepatic enzyme increased Liver function test abnormal Neutrophil count decreased White blood cell count decreased
	Uncommon	Weight decreased Blood bilirubin increased Gamma-glutamyltransferase increased Neutrophil percentage increased Protein urine Prothrombin time prolonged Pulmonary function test abnormal 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

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

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: Lipid modifying agents, other lipid modifying agents, 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

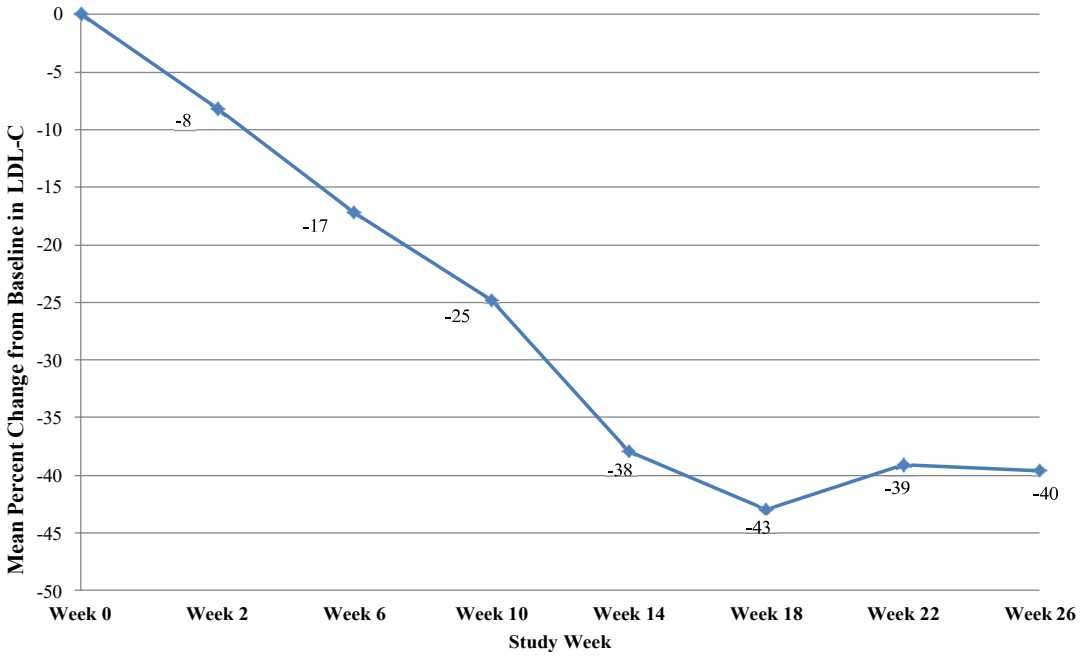
secretion and circulating concentrations of lipoprotein-borne lipids including cholesterol and triglycerides.

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 78, 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 study (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).

This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.
The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

The absolute oral bioavailability of lomitapide is 7%. Absorption is not limited by penetration of the active substance 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 study were analysed 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. Lomitapide has not been investigated in patients aged 65 years or older.

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

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

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:

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

Capsule shell:

Lojuxta 5 mg, 10 mg hard capsules
Gelatin
Titanium dioxide
Red iron oxide (E172)

Lojuxta 20 mg hard capsules
Gelatin
Titanium dioxide

Printing ink:

Shellac
Black iron oxide
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

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. MANUFACTURER

Catalent CTS
10245 Hickman Mills Drive
Kansas City
MO 64137
USA

For:
Amryt Pharma DAC
45 Mespil Road, Dublin 4,
D04 W2F1
Ireland

8. LICENSE HOLDER

Medison Pharma Ltd.
10 Hashiloach St.,
POB 7090 Petach Tikva
Israel

9. REGISTRATION NUMBERS

Lojuxta 5 mg: 152-85-33996
Lojuxta 10 mg: 152-86-33998
Lojuxta 20 mg: 152-87-33999

Revised in May 2025

Lojuxta-SPC-0324-V2