PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR LOJUXTA (LOMITAPIDE)

This is a summary of the risk management plan (RMP) for Lojuxta. The RMP details important risks of Lojuxta, how these risks can be minimised, and how more information will be obtained about Lojuxta's risks and uncertainties (missing information).

Lojuxta's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Lojuxta should be used.

This summary of the RMP for Lojuxta should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones are included in updates of Lojuxta's RMP.

I. The medicine and what it is used for

Lojuxta is authorised to treat adult patients with homozygous familial hypercholesterolaemia, an inherited disease causing high blood levels of cholesterol (a type of fat). It is used together with a low fat diet and other medicines to reduce the level of fats in the blood. The patient's disease should be confirmed by genetic testing whenever possible (see SmPC for the full indication). It contains lomitapide as the active substances and it is given orally as a capsule.

Further information about the evaluation of Lojuxta's benefits can be found in Lojuxta's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/lojuxta

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Lojuxta, together with measures to minimise such risks and the proposed studies for learning more about Lojuxta risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute ***routine risk minimisation*** measures.

In the case of Lojuxta, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Lojuxta is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Lojuxta are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lojuxta. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

SUMMARY OF SAFETY CONCERNS	
Important identified risks	Hepatic effects (elevated aminotransferases, hepatic steatosis) Gastrointestinal effects (nausea, diarrhoea, weight loss, malabsorption of fat soluble vitamins, decline in essential fatty acids) Rhabdomyolysis with or without acute renal failure due to interaction with statins
Important potential risks	Hepatic fibrosis Primary hepatic tumours Small intestinal tumours Pancreatic tumours Unintended pregnancy
Missing information	Use during pregnancy Use in the paediatric population Use with alcohol Use in non-Caucasian patients Pre-existing hepatic disease Concomitant use with potential hepatotoxic agents

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important identified risk: Hepatic effects	
Evidence for linking the risk to the medicine	Hepatic effects, such as steatosis and abnormal plasma aminotransferase levels, were common during clinical trials, and appear to be the direct result of the lomitapide mechanism of action. Hepatic effects (elevated aminotransferases, hepatic steatosis)) are considered important identified risks. (Adams, 2005 CMAJ; Bedogni, 2005 Hepatology; Browning, 2004 Hepatology; Clark, 2006 J Clin Gastroenterol; Clark, 2003 Am J Gastroenterol; Cortez-Pinto, 2004 Best Pract Res Clin Gastroenterol; Eckel, 2010 Lancet; Ghany, 2011 Harrison's Principles of Internal Medicine; Giboney, 2005 Am Fam Physician; Joy, 2008 Nat Clin Pract Cardiovasc Med; Lazo, 2011 BMJ; Shen, 2003 World J Gastroenterol; Yueh, 2011 Diabetes Res Clin Pract) There have been no cases of acute hepatotoxicity (i.e., cases that met Hy's law criteria) observed in the lomitapide clinical development programme, including the pool of Phase 2 studies conducted in over 600 subjects with elevated LDL-C and other cardiovascular risk factors, the Phase 2 HoFH study, or the Phase 3 HoFH major effectiveness study, including its long-term extension study. Across the lomitapide programme, 5 studies included an evaluation of hepatic fat. Review of scatter plots across these 5 studies showed no apparent relationship between exposure to lomitapide (based on average or nominal dose or total lomitapide dose) and maximum hepatic fat percent. In the post-marketing setting, cumulatively through 31 Jul 2020, there were 505 ICSRs reporting 764 hepatic events.
Risk factors and risk groups	There is no published evidence that untreated familial hypercholesterolaemia (FH) induces important hepatic co-morbidities. Furthermore, no specific data were retrieved regarding the epidemiology of elevated aminotransferases and hepatic steatosis in this population. Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in the United States and other Western countries, with a prevalence as high as 30% in the general population. The disease encompasses a wide spectrum of conditions, ranging from steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis (Lazo, 2011 BMJ). In the general population, increased hepatic enzymes may be detected in up to 4% of asymptomatic subjects (Giboney, 2005 Am Fam Physician). A US study of 15,676 adults above 17 years of age found elevated ALT or AST in 7.9% of subjects (Clark, 2003 Am J Gastroenterol). Interestingly, only 1/3 of them had a medical history that could obviously explain this finding (i.e., high alcohol consumption, viral hepatitis or iron overload). In the remaining

Important identified risk: Hepatic effects	
	cases, the study revealed an association between increased ALT or AST and higher body mass index, triglycerides, fasting insulin, and lower high-density lipoprotein (HDL). Women with type 2 diabetes and hypertension were also more likely to have abnormal hepatic enzymes. Major risk factors for liver disease include alcohol abuse, long-term exposure to various medications (including herbal compounds, birth control pills, and over-the-counter medications), sexual promiscuity, extensive travelling, exposure to jaundiced or other high-risk persons, recent surgery, remote or recent transfusion with blood and blood products, and family history of liver disease (Ghany, 2011 Harrison's Principles of Internal Medicine). With regard to elevated aminotransferases of non-specific origin, an epidemiological study using data from the Third US Health and Nutrition Examination Survey identified the following risk factors: higher body mass index, triglycerides, fasting insulin, and lower HDL (in both sexes), type 2 diabetes and hypertension (in women only) (Clark, 2003 Am J Gastroenterol). All these parameters may indicate the presence of metabolic syndrome, which is diagnosed when at least three of the following criteria are met: increased waist circumference, increased triglycerides, reduced HDL cholesterol, increased blood pressure, and increased fasting glucose (Eckel, 2010 Lancet). A significant correlation between metabolic syndrome and abnormal ALT was seen in a recent study of 1,313 Taiwanese subjects (Yueh, 2011 Diabetes Res Clin Pract). Insulin resistance, obesity, diabetes and dyslipidaemia are also risk factors for hepatic steatosis (Cortez-Pinto, 2004 Best Pract Res Clin Gastroenterol). The incidence of hepatic AEs and elevated aminotransferases was examined to determine if the type of co-administered statin drug appeared to influence the risk of these events. No clear association between the type of concomitant statin and the incidence, type, or severity of hepatic AEs or laboratory abnormalities during treatment with lomitapide was observed. Because 27 of the 29 patients in the Phase 3 study were on statins, the influence of concomitant statins on hepatic AEs is unknown.
Risk minimisation measures	Routine risk communication • SmPC section 4.3. Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Additional pharmacovigilance activities	Restricted medical prescription. Educational material for prescribers and patients.

Important identified risk: Gastrointestinal effects (nausea, diarrhoea, weight loss, malabsorption of fat soluble vitamins, decline in essential fatty acids)	
Evidence for linking the risk to the medicine	The AEs most frequently reported across the entire program were of GI origin and included diarrhoea, abdominal distension, and vomiting. GI effects (nausea, diarrhoea, weight loss, malabsorption of fat-soluble vitamins, and decline in essential fatty acids) and are considered an important identified risk. (Bharucha, 2007 The Merck Manual for Health Care Professionals; Britt, 2007 Aust Fam Physician; Feldman, 1994 Epidemiol Infect; Greenberger, 2008 The Merck Manual for Health Care Professionals; Ruiz, 2008 The Merck Manual for Health Care Professionals; Samaha, 2008 Nat Clin Pract Cardiovasc Med; Thomas, 2003 Gut; Yamanaka, 1980 Prog Lipid Res) In the clinical development program, in Study UP1001, 5 patients experienced gastrointestinal disorders (83.3%) and in study UP1002 (AEGR-733-005), 27 patients experienced gastrointestinal disorders (93.1%) In the post-marketing setting, cumulatively, through 31 Jul 2020, there were 1673 ICSRs (1218 solicited, 436 spontaneous, 19 literature) reporting 3069 GI events.
Risk factors and risk groups	There are multiple possible causes of nausea and/or vomiting, such as disorders of the GI tract (bowel obstruction, hepatitis, gastroenteritis, gastroparesis), central nervous system (head injury, brain haemorrhage, increased intracranial pressure, migraine, motion sickness), or systemic (drug adverse reaction, cancer, diabetic ketoacidosis, liver or renal failure, pregnancy, severe pain) (Greenberger, 2008 The Merck Manual for Health Care Professionals). Acute diarrhoea may result from infections, food poisoning or adverse reaction to medications. The causes of chronic diarrhoea are more complex and, in addition to drugs, include cancer (gastrointestinal or endocrine), irritable bowel syndrome, carbohydrate intolerance, inflammatory bowel disease, malabsorption syndromes, surgery and hyperthyroidism (Bharucha, 2007 The Merck Manual for Health Care Professionals).
Risk minimisation measures	Routine risk communication • SmPC section 4.2. • SmPC section 4.3. Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.

Important identified risk: Gastrointestinal effects (nausea, diarrhoea, weight loss, malabsorption of fat soluble vitamins, decline in essential fatty acids)	
Additional pharmacovigilance activities	Restricted medical prescription. Educational material for prescribers and patients.

Important identified risk: Rhabdomyolysis with or without acute renal failure due to interaction with statins	
Evidence for linking the risk to the medicine	Drug interaction studies indicated that lomitapide 60 mg increased simvastatin levels by a factor of 1.7 when the 2 drugs were co-administered. Because lomitapide is indicated as an adjunct to other lipid lowering treatments (and statins are commonly prescribed in patients with HoFH), this interaction was considered to be an important risk. (Ghany, 2011 Harrison's Principles of Internal Medicine; Khan, 2009 Neth J Med; Simvador, 2010 Summary of Product Characteristics) In the clinical development programme: The incidence of hepatic AEs and elevated aminotransferases was examined to determine if the type of co-administered statin drug appeared to influence the risk of these events. No clear association between the type of concomitant statin and the incidence, type, or severity of hepatic AEs or laboratory abnormalities during treatment with lomitapide was observed. Because 27 of the 29 patients in the Phase 3 study were on statins, the influence of concomitant statins on hepatic AEs is unknown. In the post-marketing setting, cumulatively up to 31 Jul 2020, there were 2 spontaneous cases of potential interaction between lomitapide and statins. The first case reported additionally serious events of Cardiac failure congestive, Cerebral haemorrhage, Cerebrovascular accident, Haemorrhage, Haemorrhagic stroke, Hepatotoxicity, Hypovolaemic shock, International normalised ratio increased, Liver function test increased, Myocardial infarction, and Subdural haematoma. The second case reported a non-serious event of Liver function test increased.
Risk factors and risk groups	Risk factors for rhabdomyolysis/myopathy are numerous, including blunt trauma, certain toxins (such as addictive psychoactive drugs and carbon monoxide) and medications (such as statins and fibrates), prolonged immobilisation, excessive muscular activity, temperature extremes, muscle ischaemia, infections, electrolyte imbalances and genetic disorders (Khan, 2009 Neth J Med). The risk factors for liver disease are discussed under “Identified Risk: Hepatic events” of this Module VII.
Risk minimisation measures	Routine risk communication • SmPC section 4.3. Routine risk minimisation activities recommending specific clinical measures to address the risk:

Important identified risk: Rhabdomyolysis with or without acute renal failure due to interaction with statins	
	• SmPC section 4.5. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Additional pharmacovigilance activities	Restricted medical prescription. Educational material for prescribers and patients.

Important potential risk: Hepatic fibrosis	
Evidence for linking the risk to the medicine	Clinical Study: No cases of hepatic fibrosis were observed in CTs with lomitapide. Post-marketing experience: Cumulatively, up to 31 Jul 2020, were 2 cases of serious hepatic fibrosis.
Risk factors and risk groups	Liver fibrosis results from continuous damage to the liver, such as that caused by viral hepatitis, alcohol abuse, drugs (e.g. amiodarone, chlorpromazine, isoniazide, methotrexate, methyldopa, tolbutamide), metabolic diseases involving an overload of iron or copper, autoimmune diseases, or congenital abnormalities (Balsano, 2009 Curr Drug Targets; Shaffer, 2007 The Merck Manual for Healthcare Professionals). Metabolic syndromes, such as obesity, insulin resistance, and type 2 diabetes, represent strong risk factors in the development of fatty liver disease and related fibrosis (Balsano, 2009 Curr Drug Targets).
Risk minimisation measures	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Additional pharmacovigilance activities	Restricted medical prescription. Educational material for prescribers and patients.

Important potential risk: Primary hepatic tumours	
Evidence for linking the risk to the medicine	In a 2-year carcinogenicity study in mice, increased incidences of liver and small intestinal tumours occurred at exposures (AUC) to lomitapide relevant to those in humans at 60 mg. Because lomitapide was not genotoxic, it was concluded that these tumours were secondary to a non-genotoxic

Important potential risk: Primary hepatic tumours	
	mechanism. In addition, an increased incidence of benign pancreatic acinar cell adenoma was observed in high-dose male rats at an exposure 6 times that in humans at the 60 mg dose. As the relevance of these findings for humans is unknown, primary hepatic, small intestinal and pancreatic tumours are included as important potential risks. Clinical Study: No cases of benign or malignant liver neoplasms were observed with lomitapide. Post-marketing experience: Cumulatively, 1 case reporting Primary hepatic tumour has been reported from the post marketing sources up to 31 Jul 2020. This serious solicited case concerned a 67-year-old female patient who was diagnosed (about 3 years after starting lomitapide treatment) with serious events of pancreatic and hepatic carcinoma stage IV. Six months after being diagnosed with cancer, the patient passed away.
Risk factors and risk groups	Hepatocellular carcinoma is associated with cirrhosis in 50% to 80% of patients; 5% of cirrhotic patients eventually develop hepatocellular cancer, which is often multifocal. Other major risk factors include a history of hepatitis B or C, obesity and eating foods tainted with aflatoxin (National Cancer Institute, 2011a).
Risk minimisation measures	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 5.3. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Additional pharmacovigilance activities	Restricted medical prescription.

Important potential risk: Small intestinal tumours	
Evidence for linking the risk to the medicine	In a 2-year carcinogenicity study in mice, increased incidences of liver and small intestinal tumours occurred at exposures (AUC) to lomitapide relevant to those in humans at 60 mg. Because lomitapide was not genotoxic, it was concluded that these tumours were secondary to a non-genotoxic mechanism. In addition, an increased incidence of benign pancreatic acinar cell adenoma was observed in high-dose male rats at an exposure 6 times that in humans at the 60 mg dose. As the relevance of these findings for humans is unknown, primary hepatic, small intestinal and pancreatic tumours are included as important potential risks. Clinical Study: No cases of benign or malignant intestinal neoplasms were observed in Clinical Studies.

Important potential risk: Small intestinal tumours	
	Post marketing experience: One case reporting a small intestine carcinoma was identified up to 31 Jul 2020. This solicited case concerned a 63-year-old female patient. Relevant risk factors included patient's medical history of cervical cancer, glandular cancer, and Meckel diverticulum. However, due to the plausible temporal association between the onset of the small intestine carcinoma (outcome unknown) and the administration of lomitapide, the causal relationship cannot be completely excluded. Of note, the treatment was resumed at the same dosage as prior to the hospitalization for the intestinal carcinoma, thus making the causal association more doubtful.
Risk factors and risk groups	Risk factors for small intestinal cancer include a high fat diet, Crohn's disease, celiac disease and familial adenomatous polyposis (FAP) (Hoofnagle, 2011 Am J Physiol Heart Circ Physiol; National Cancer Institute, 2011c).
Risk minimisation measures	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 5.3. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Additional pharmacovigilance activities	Restricted medical prescription.

Important potential risk: Pancreatic tumours	
Evidence for linking the risk to the medicine	In a 2-year carcinogenicity study in mice, increased incidences of liver and small intestinal tumours occurred at exposures (AUC) to lomitapide relevant to those in humans at 60 mg. Because lomitapide was not genotoxic, it was concluded that these tumours were secondary to a non-genotoxic mechanism. In addition, an increased incidence of benign pancreatic acinar cell adenoma was observed in high-dose male rats at an exposure 6 times that in humans at the 60 mg dose. As the relevance of these findings for humans is unknown, primary hepatic, small intestinal and pancreatic tumours are included as important potential risks. No cases of benign or malignant pancreatic neoplasms were observed in CTs. Post-marketing experience: One case of Primary pancreatic tumour was identified up to 31 Jul 2020. This serious solicited case concerned a 67-year-old female patient who was diagnosed (about 3 years after starting lomitapide treatment) with serious events of pancreatic and hepatic carcinoma stage IV. Six months after being diagnosed with cancer, the

Important potential risk: Pancreatic tumours	
	patient passed away. Note, this is the same case described in Hepatic Tumours.
Risk factors and risk groups	Most pancreatic cancers have mutations in genes KRAS, p53 and p16, which are associated with the control of tumour growth. BRCA2 mutations have also been involved in some pancreatic cancers (European Society for Medical Oncology, 2012). Known risk factors for pancreatic cancer include a family history of the disease (between 10% and 20% of pancreatic cancers may have a familial component), cigarette smoking (25% of patients with pancreatic cancer are or have been long-term cigarette smokers), obesity and chronic pancreatitis (European Society for Medical Oncology, 2012). Furthermore, the risk of pancreatic cancer increases considerably with age. More than 8 out of 10 cases (80%) are diagnosed in people aged 60 and over, whilst people younger than 40 are rarely affected (Cancer Research UK, 2013).
Risk minimisation measures	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 5.3. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Additional pharmacovigilance activities	Restricted medical prescription.

Important potential risk: Unintended pregnancy	
Evidence for linking the risk to the medicine	In an oral study of embryofoetal development, lomitapide was administered to presumed-pregnant rats on days 6 through 15 of gestation at doses of 0.04, 0.4, or 4 mg/kg. Lomitapide caused foetal malformations (abdomen, tail, heart, limbs or paws, and anus as well as delays in ossification of the cranial, vertebral, and pelvic bones) at 0.4 and 4 mg/kg and maternal toxicity at 4 mg/kg, and is therefore considered teratogenic in rats. By contrast, lomitapide was not teratogenic in an embryofoetal development study in rabbits at oral doses up to 10 mg/kg. In an oral study to evaluate fertility and general reproduction in rats, no adverse effects on reproduction were observed in males at doses of 0.2, 1, or 5 mg/kg or in females at doses of 0.04, 0.2, or 1 mg/kg. Lomitapide was teratogenic in rats in the absence of maternal toxicity at an exposure (AUC) estimated to be less than that in humans at 60 mg. Since

Important potential risk: Unintended pregnancy	
	pregnant women were not included in clinical studies with lomitapide, the potential risk for humans is unknown No cases of unintended pregnancy were identified in clinical trials with lomitapide. The have been 16 reports of pregnancy up to 31-Jul-2020, four of which were unintended pregnancy and concerned birth of live premature infant who developed fatal nosocomial infection which was not related to lomitapide, 1 was terminated via abortion due to social reasons, and 2 resulted in healthy infants.
Risk factors and risk groups	Lomitapide may induce diarrhoea and vomiting and thus decrease the absorption of oral contraceptives. All women of reproductive age using oral contraceptives may be affected, as diarrhoea and vomiting were among the most common GI disorders associated with lomitapide treatment. They occurred in 80% and 34% of HoFH subjects, respectively.
Risk minimisation measures	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4. • SmPC section 4.5. • SmPC section 4.6. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Additional pharmacovigilance activities	Restricted medical prescription. Educational material for prescribers and patients.

Missing information: Use during pregnancy	
Risk minimisation measures	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.6. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Additional pharmacovigilance activities	Restricted medical prescription. Educational material for prescribers and patients.

Missing information: Use in the paediatric population	
Risk minimisation measures	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.2. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Additional pharmacovigilance activities	Restricted medical prescription.

Missing information: Use with alcohol	
Risk minimisation measures	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Additional pharmacovigilance activities	Restricted medical prescription. Educational material for prescribers and patients.

Missing information: Use in non-caucasian patients	
Risk minimisation measures	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 5.2. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Additional pharmacovigilance activities	Restricted medical prescription.

Missing information: Pre-existing hepatic disease	
Risk minimisation measures	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 5.2. Other routine risk minimisation measures beyond the Product Information:

Missing information: Pre-existing hepatic disease	
	Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Additional pharmacovigilance activities	Restricted medical prescription. Educational material for prescribers and patients.

Missing information: Concomitant use with potential heptatotoxic agents	
Risk minimisation measures	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Additional pharmacovigilance activities	Restricted medical prescription. Educational material for prescribers and patients.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

Lomitapide Observational Worldwide Evaluation Registry (LOWER)

Study short name and title:

A registry has been set up to evaluate the long-term safety and effectiveness of lomitapide in clinical practice.

To evaluate whether prescribers of lomitapide enrolled at registry sites are following the screening and monitoring recommendations as specified in the product information (PI) and the prescriber educational materials aimed at risk minimisation.

Rational and study objectives:

The objectives of the registry are:

· To evaluate the occurrence of the following in patients treated with lomitapide:

o Hepatic abnormalities

o Gastrointestinal (GI) events

o Small bowel, hepatic, colorectal and pancreatic tumours

o Events associated with coagulopathy

o Major Adverse Cardiovascular Events (MACE) events

- o Death, including cause of death
- · 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. The outcome of primary interest is major congenital anomalies. Refer to Section 7.2.3 of the LOWER protocol for more detail.
- · To evaluate the long-term effectiveness of lomitapide in maintaining control of serum lipid levels in clinical practice.
- · To evaluate whether prescribers of lomitapide enrolled at study sites are following the screening and monitoring recommendations as specified in the product information (PI) and the prescriber educational materials aimed at risk minimisation.
- · To evaluate the safety risks related to the use of alcohol in patients treated with lomitapide.
- · To evaluate safety data concerning the use of lomitapide in non-Caucasian patients.
- · To evaluate the safety of lomitapide in patients with pre-existing hepatic disease.
- · To evaluate the safety of lomitapide in patients concomitantly treated with potentially hepatotoxic agents.

LILITH study

Study short name and title:

Evaluation of the effect of lomitapide treatment on major adverse cardiovascular event (MACE) in patients with homozygous familial hypercholesterolemia (HoFH).

Rationale and study objectives:

Primary objective:

The primary objective of the study is to evaluate the occurrence of MACE after three years of treatment with lomitapide as compared to the occurrence of MACE during three years before the initiation of lomitapide.

Secondary objectives:

To evaluate the changes of LDL-C and other lipoproteins at one, two and three years of lomitapide treatment and the correlation of these laboratory evaluations with changes in MACE occurrence

To evaluate changes in the levels of AST, ALT, GGT at one, two and three years of lomitapide treatment, as measures of safety

To evaluate the discontinuation of LDL apheresis during follow-up and the adherence to lipid-lowering medications (including lomitapide).

Study design:

Multicenter, open-label, retrospective and prospective study

Study population:

HoFH patients over the age of 18 years will be enrolled through a network of lipid centres.

Milestones:

Final study report to be submitted by 30 Jun 2027.

II.C.2 Other studies in post-authorisation development plan

There are no other studies in the post-authorisation development plan.