Chiesi [redacted]

RISK MANAGEMENT PLAN

LOJUXTA (LOMITAPIDE)

RMP Version Number: **8.0**

Data Lock Point for this RMP: **31 July 2024**

[redacted]

Chiesi [redacted]

EU RISK MANAGEMENT PLAN FOR LOJUXTA (LOMITAPIDE) CAPSULES:

RMP version to be assessed as part of this application:

RMP Version number:	8.0
Data lock point for this RMP:	31 July 2024
Date of final sign off:	07 April 2026

Rationale for submission of an updated RMP:

- To support a safety variation to include paediatric population as an approved age group of lomitapide administration upon the completion of the APH-19 clinical trial and to introduce a 2 mg capsule as an extension of the dosage for the paediatric population.

Summary of significant changes in the RMP:

- Extension of the currently approved indication to paediatric patients aged 5 years and older with homozygous familial hypercholesterolaemia (HoFH).
- New paediatric dosage
- LOWER registry removed as Additional Pharmacovigilance Activity Category 2 and replaced with Annual safety and efficacy report.

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

Version number:	7.0
Approved with procedure:	EMEA/H/C/002578/II/0046
Date of approval (opinion date):	24-Feb-2022

QPPV name: Stella Fiorini
QPPV Office Department Head & QPPV

Global Regulatory Affairs and Patient Safety

QPPV signature: [redacted]

The content of this RMP has been reviewed by the marketing authorisation Chiesi's QPPV. The electronic signature is available on file.

Table of Contents

List of Tables

List of Abbreviations

TERM	EXPLANATION
AE	Adverse event
ALT	Alanine transferase (synonymous with glutamate pyruvate-transaminase, GPT)
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate transferase (synonymous with glutamate oxalacetate-transaminase, GOT)
ATC	Anatomical therapeutic classification
AUC	Area under the plasma drug concentration-time curve
BMI	Body mass index
CCSI	Company core safety information
CHD	Coronary heart disease
CI	Confidence interval
Cmax	Maximum concentration of drug in plasma
CTD	Common Technical Document
CYP	Cytochrome
DB	Double-blind
DHPC	Direct healthcare professional communication
DLP	Data lock point
EEA	European Economic Area
e.g.	For example
EPAR	European Public Assessment Reports
EU	European Union
GGT	Gamma-glutamyl-transferase
GOT	Glutamate-oxalacetate-transaminase
GPT	Glutamate-pyruvate-transaminase
GPS	Global Patient Safety
h	Hours
HoFH	Homozygous familial hypercholesterolaemia
IBD	International birth date
ICSR	Individual Case Safety Report
INN	International non-proprietary name
LDL	Low-density lipoprotein
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
n.a.	Not applicable
MTP	Microsomal triglyceride transfer protein
OL	Open-label
PASS	Post Authorisation Safety Study
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamics
PK	Pharmacokinetics

TERM	EXPLANATION
PL	Patient leaflet
PSUR	Periodic Safety Update Report
PT	Preferred Term
QD	Once daily
QPPV	Qualified person for pharmacovigilance (for the EU)
RMP	Risk Management Plan
SD	Standard deviation
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
UK	United Kingdom
US	United States
vs.	Versus

PART I PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) (INN or common name)	Lomitapide
Pharmacotherapeutic group(s) (ATC Code)	C10AX12
Marketing Authorisation Holder	Chiesi Farmaceutici S.p.A.
Medicinal products to which this RMP refers	Lojuxta
Invented name(s) in the European Economic Area (EEA)	Lojuxta
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class** Lomitapide is a member of the class of benzamides obtained by formal condensation of the carboxy group of 4'-(trifluoromethyl) biphenyl-2-carboxylic acid with the primary amino group of 9-[4-(4-aminopiperidin-1-yl)butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide. **Summary of mode of action** Lomitapide is a selective inhibitor of microsomal triglyceride transfer protein (MTP). MTP is an intracellular lipid-transfer protein found in the lumen of the endoplasmic reticulum that is responsible for binding and shuttling individual lipid molecules between membranes (Hussain, 2003 J Lipid Res; Liao, 2003 Journal of lipid research). 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. (Liao, 2003 Journal of lipid research). Lomitapide is used (as its mesylate salt) as a complement to a low-fat diet and other lipid-lowering treatments in patients with homozygous familial hypercholesterolaemia. It has a role as an anticholesteraemic drug and a MTP inhibitor. (NIH PubChem Lomitapide). **Important information about its composition** Pharmacotherapeutic group: Lipid modifying agents, other lipid modifying agents, ATC code: C10AX12.

Hyperlink to the Product Information	Module 1.3.1
Indication(s) in the EEA	**Current** 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 hyperlipoproteinaemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism) must be excluded. **Proposed** 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 for the treatment of adult and paediatric patients aged 5 years and older with homozygous familial hypercholesterolaemia (HoFH). Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinaemia and secondary causes of hypercholesterolaemia (e.g. nephrotic syndrome, hypothyroidism) must be excluded.
Dosage in the EEA	**Current** 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. 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. **Proposed** *Adults*

The recommended starting dose for adult patients 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.

Paediatric patients (aged 5 to 10 years)

The recommended starting dose for children aged 5 to 10 years is 2 mg once daily. After 8 weeks the dose may be increased, according to LDL-C response and based on acceptable safety and tolerability, to 5 mg and then, at a minimum of 4-week intervals, to 10 mg and to the maximum recommended dose of 20 mg (see section 4.4). The dose may be further increased to 30 mg, if safety and tolerability permit, after a minimum of 6 months from start of treatment.

Paediatric patients (aged 11 to 15 years)

The recommended starting dose for children aged 11 to 15 years is 2 mg once daily. After 4 weeks the dose may be increased, according to LDL-C response and based on acceptable safety and tolerability, to 5 mg and then, at a minimum of 4-week intervals, to 10 mg, 20 mg, and to the maximum recommended dose of 40 mg.

Paediatric patients (aged 16 to 17 years)

The recommended starting dose for children aged 16 to 17 years is 5 mg once daily. After 4 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 and to the maximum recommended dose of 40 mg.

The recommended starting doses, timings and increments of dose increases for paediatric patients are summarised in Table 1.

Table 1: Lomitapide starting dose and dose escalation by paediatric age group

	Lomitapide Dose (mg)					
Age Group	**Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Maximum Recommended**
5 to 10 years	2	2	5	10	20	20*
11 to 15 years	2	5	10	20	40	40
16 to 17 years	5	10	20	40	40	40

	*If sufficient clinical response is not seen after 6 months of treatment the physician can consider a dose increase to 30 mg/day, if safety and tolerability permit. *Adults and paediatric patients (aged 5 to 17 years)* The dose should be escalated gradually to minimise the incidence and severity of gastrointestinal adverse reactions and aminotransferase elevations. For paediatric patients, when a patient crosses over into the next age category, the dose of lomitapide can be escalated to the maximum recommended dose applicable for the new age category. It is recommended to exercise caution in paediatric patients who have a low body weight or height for their age (<15 kg or BMI and height <10th percentile according to WHO Growth Charts for Boys and Girls 5 to 19 Years of Age).
Pharmaceutical form(s) and strengths	**Current** 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. 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. 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. 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. 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. 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. **Proposed** The capsule is a grey cap/grey body hard capsule of 19.4 mm, printed with black ink imprinted with “2 mg” on body and “A733” on cap. 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. 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. 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.

Is/will the product be subject to additional monitoring in the EU?	Yes

PART II SAFETY SPECIFICATION

PART II MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

Indication

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 for the treatment of adult and paediatric patients aged 5 years and older with homozygous familial hypercholesterolaemia (HoFH).

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

Incidence and Prevalence

HoFH is a rare, life-threatening, genetic disorder of cholesterol metabolism, which leads to very high levels of LDL-C in the blood and markedly reduced life expectancy compared to the general population and patients with the related disorder, heterozygous familial hypercholesterolaemia (HeFH). Under normal circumstances, LDL particles bind to the LDL receptor (LDLR) present on cell surfaces (most notably on hepatic cells) and are removed from plasma via endocytosis (Hegele, 2001 Am J Hum Genet). However, receptor dysfunction or attributes of the LDL particle can impact LDL-LDLR interactions, leading to decreased uptake of LDL from the blood.

The LDLR plays a critical role in regulating the amount of cholesterol in the blood. Historically, HoFH was thought to be caused by homozygosity or compound heterozygosity for mutations in LDLR, leading to impairment of LDLR function. However, it is now estimated that LDLR gene loss-of-function variants account for 85%-90% of HoFH cases, with recent advances highlighting the prevalence and heterogeneity of the genetic defects underlying HoFH and its clinical phenotype. HoFH phenocopies have been found to be caused by mutations in alleles of the genes for proteins associated with LDLR (Cuchel, 2023 Eur Heart J, Sjouke, 2016 J Clin Lipidol):

- Apo B is the main protein on LDL and binds LDLR during the LDL uptake process. Mutations in APOB have been found in 5%-10% of HoFH cases,
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a key protein in the post translational inhibition of LDLR, targeting the LDLR for degradation instead of recycling. PCSK9 gain-of-function variants account for 1%-3% of HoFH cases,
- LDLR adapter protein 1 (LDLRAP1) is involved in the endocytosis of the LDLR-LDL-C lipoprotein complex. LDLRAP1 loss-of-function variants have been found in <1% of cases) (Autosomal Recessive Hypercholesterolaemia [ARH]).

Emerging studies suggest that the prevalence of HeFH, and consequently HoFH, may be higher than previously thought. Historically, the prevalence of clinical HoFH had been estimated at 1 per million. However, global prevalence of HoFH is estimated at between 1:250,000 to 1:360,000 in the most recently published European treatment guideline (Cuchel, 2023 Eur Heart J), with an estimated 23,000 new cases worldwide (Tromp, 2022, Lancet), while recent studies in unselected general populations suggest an estimated prevalence of HeFH of approximately 1 case in 250 individuals (Akioyamen, 2017 BMJ Open). A recent worldwide meta-analysis of 11 million subjects produced an estimate that was

roughly in line with those cited in the European guideline (Beheshti, 2020, J Am Coll Cardiol). Prevalence data are, however, continuing to evolve, and these calculations could be an under-estimation or over-estimation in the general patient population.

In addition, founder effect (a phenomena of reduction in genetic variation that results when a small subset of a large population is used to establish a new colony while the new population may be very different from the original population, both in terms of its genotypes and phenotypes) make the prevalence of HoFH more common in specific populations, and the prevalence of HoFH in a given region may be highly dependent on its demographics.

Demographics of the population in the authorised indication - age, gender, racial and/or ethnic origin and risk factors for the disease

Adult patients diagnosed with HoFH may have LDL-C values of 650 to >1,000 mg/dL. Paediatric HoFH patients, despite their young age, may also present with similarly elevated LDL-C levels to those seen in adults. The severity of the elevated LDL-C levels in paediatric HoFH patients is illustrated in published literature. For example, in a study of 17 paediatric patients with HoFH (Klaus, 2018 Pediatr Nephrol), the mean LDL-C concentration at diagnosis, prior to commencement of lipid lowering therapy (LLT), was 756 mg/mL± 206 mg/dL (mean age at diagnosis was 5.8 years ±2.5 years). LDL-C levels in paediatric HoFH patients may even exceed 1,000 mg/dL; in published studies reporting the off-label use of Lojuxta in paediatric HoFH patients (Chacra, 2019 *J Clin Lipidol*, Kolovou, 2019, JACC Case Rep)

HoFH has been observed in all major ethnic groups, but prevalence may be at least 10-fold higher in some populations (such as French Canadians, Afrikaners in South Africa, or Christian Lebanese) due to founder effects. (Cuchel, 2023 Eur Heart J)

HoFH is a genetic disorder. The only identifiable risk factor for this hereditary disease is family history. As stated above, this risk will be increased in certain ethnic groups.

The main existing treatment options

Several treatment options exist for reducing LDL-C in patients with HoFH including lipid-lowering medications, LDL apheresis (LA), and liver transplantation. The EAS 2023 guidelines recommend that newly diagnosed HoFH patients commence treatment on a high-intensity statin and ezetimibe. Within 8 weeks from start of treatment with statins and ezetimibe PCSK9-directed therapy (at approved doses for HoFH) should be considered where available. If patients show >15% additional LDL-C reduction, PCSK9-directed therapy may be continued, but if response is poor, clinicians should consider stopping this therapy. Subsequent options include LDLR–independent therapies, such as lomitapide or evinacumab and/or LA (Cuchel, 2023 Eur Heart J).

While the majority of historically recommended HoFH treatments (such as statins, ezetimibe, PCSK-9 inhibitors and LA) are still included in the recent update to European treatment guidelines (Cuchel, 2023 Eur Heart J), it is worth noting that the 2023 update omits recommendations over the use of bile acid sequestrants (used in combination with statins to lower cholesterol) in non-pregnant/non-lactating individuals. This contrasts with the previous 2014 HoFH guidelines (Cuchel, 2014, Eur Heart J), where bile acid sequestrants (in combination with statins) were a suggested treatment, but with caveats against tolerability and availability. Indeed, in the current 2023 treatment guidelines, bile acid sequestrants are only referred to in the context of treating pregnant or lactating HoFH patients (for whom statins are contraindicated), with caveats against efficacy and tolerability.

The addition of LDLR-independent therapies to the treatment landscape has been a significant step forward in the treatment of this disease over the last decade. Still, at present there is only one LDLR-independent therapy licensed in the EU for the treatment of paediatric patients aged 5 years and above

(evinacumab) with an intravenous route of administration. Evinacumab received a positive opinion from the CHMP in November 2024 to extend the indication to children aged 6 months and older (EC Decision issued on 13 December 2024).

Other measures such as exercise and abstaining from smoking will have cardiovascular benefits and should be recommended in an attempt to reduce other risk factors for cardiovascular morbidity.

Natural history of the indicated condition in the population, including mortality and morbidity

The symptoms of HoFH start early in life: HoFH plasma LDL-C levels are chronically and extremely elevated from birth or even in utero (McErlean, 2023 BMJ), with premature CVD, atherosclerosis and aortic stenosis developing as early as in childhood, and the high risk of an early cardiac-related death if patients are left untreated (Thompson, 2018 Eur Heart J).

Despite young age, patients with HoFH often initially present with extensive xanthomas on the skin, joints and tendons, prompting further medical investigation and the subsequent HoFH diagnosis.

Cardiovascular disease (CVD) results in a number of fatal and nonfatal events, including myocardial infarction (MI) and stroke, and is the leading cause of death and a major cause of disability in the United States (US) (Curtin, 2023, Natl Vital Stat Rep), the European Union (EU) (EuroStat – monthly statistics; causes of death 2019-2020) and most industrialized nations. While a number of risk factors for CVD have been identified (including smoking, physical inactivity, obesity, high blood pressure, and diabetes), elevated plasma cholesterol, primarily in the form of LDL-C, is estimated to account for a significant portion of the CVD burden.

Elevated LDL-C is a critical risk factor for developing accelerated premature and progressive atherosclerotic cardiovascular disease (ASCVD), resulting in coronary heart disease (CHD), which is reflected in figures from the World Health Organisation which estimate that approximately 60% of CVD events resulting from coronary heart disease (CHD) and approximately 20% of strokes can be attributed to elevated cholesterol.

Important co-morbidities

Concomitant medication(s) in the target population

Concomitant medications in the target population include:

- Other lipid lowering agents (statins, ezetimibe, cholesterol absorbing inhibitors)
- PCSK-9 inhibitor over 10 years of age
- LDL-R independent therapy (evinacumab)
- Medications aimed at treating the cardiovascular complications of HoFH including:
    - Anticoagulants
    - Antihypertensives
    - Anti-arrhythmics
    - Anti-platelet agents
    - Anti-anginal medications
- Medications for other conditions occurring in the age group of patients but not related to HoFH. As this condition affects a young age group, the target population may require medication for common conditions which occur in this age group including:

- Antibiotics
- Oral contraception
- Anti-fungal agents

Important co-morbidities found in the target population

Cardiovascular disorders including atherosclerosis, angina pectoris, myocardial infarction, transient ischaemic attacks, aortic stenosis, heart valve disease and peripheral artery occlusive disease, represent the largest co-morbidity in patients with HoFH and lipid-lowering therapy is associated with delayed cardiovascular events and prolonged survival in these patient populations (Citkowitz, 2012; Hegele, 2001 Am J Hum Genet; Jaeger, 2002 J Pediatr; Raal, 2011 Circulation).

Kolansky and colleagues studied a large cohort of 39 HoFH patients (Kolansky, 2008 Am J Cardiol). CVD was clinically evident in 88% of subjects aged >16 years and 9% of those <16 years. Markers of atherosclerosis correlated significantly with the age at which lipid-lowering treatment was initiated. Twenty of 22 children had no clinical evidence of coronary artery disease, yet 7 of these children had mild coronary artery disease (<50%) and 8 had mild to moderate aortic regurgitation. During follow-up, 7 children developed progression of coronary and/or aortic valvular disease during their teenage years and 4 required surgical interventions.

In the study by Kolansky and colleagues, CVD symptoms first appeared in most HoFH patients in decades 2 and 3 of life (Kolansky, 2008 Am J Cardiol). The exceptions were 2 children who were <10 years and 2 adults who were >30 years when CVD first became clinically apparent. They noticed a clear difference in the presence of an established diagnosis of CVD based on age. Cardiovascular evaluation confirmed that the older group had more advanced CVD compared with younger subjects.

Cardiovascular disorders are the main cause of mortality in HoFH patients. In a retrospective study of 149 HoFH subjects, 65 deaths occurred during the monitored period of 37 years (1972 – 2009). Among these, 50 deaths (77%) were due to cardiovascular events (Raal, 2011 Circulation). However, advances in lipid-lowering therapy were directly associated with reduction in mortality in subjects with HoFH (Raal, 2011 Circulation).

Epidemiologic data clearly support the link between hypercholesterolaemia and CVD risk; the importance of hypercholesterolaemia as one of the main independent cardiovascular risk factors was established in the 1960s and there is now substantial evidence from observational and large registry based studies, clinical trials, models, and meta-analyses, showing the causal and dose-related roles of LDL-C elevation for atherosclerosis development, and atherosclerotic cardiovascular disease (ASCVD), and the benefits of early reduction in LDL-C levels on CVD prevention (Groselj, 2022, Eur Heart J; Sanchez-Ramos, 2021 Atherosclerosis; Hu, 2020 Circulation; Ference, 2017 Eur Heart J; Krogh, 2016, Eur Heart J). In individuals who are genetically predisposed to hypercholesterolaemia (Familial Hypercholesterolaemia [FH]) and who have lifelong elevated LDL-C levels, the process of atherosclerosis is accelerated and can lead to a 10-times excess risk of premature CVD (Groselj, 2022, Eur Heart J).

PART II MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Toxicity

Key issues identified from acute or repeat-dose toxicity studies

Repeat-dose Toxicity (hepatic effects, pulmonary histiocytosis)

Rat studies

Lipid accumulation in the liver and/or small intestine was observed in a 1-month oral study in rats at doses of 0.5, 5, and 50 mg/kg. This change generally was reversible following a 1-month post-dose period. Similar effects on the liver and/or small intestine were noted in a 6-month toxicity study in rats at doses of 0.02, 0.2, 2, and 20 mg/kg. Additional findings in the 6-month study included subacute inflammation and single-cell necrosis in the liver and pulmonary histiocytosis at doses ≥ 0.2 mg/kg. Importantly, the results of a 6-month oral investigative study in rats given lomitapide at 2 mg/kg (the only dose tested) showed that the changes observed in the liver, small intestine, and lung were reversible.

Dog studies

The same pattern of lipid accumulation in the liver and/or small intestine was observed in two oral toxicity studies in dogs: at doses of 0.2, 2, and 20 mg/kg in a 1-month study and at doses of 0.01, 0.1, 1, and 10 mg/kg in a 6-month study. Mild to marked increases in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) associated with single-cell necrosis in the liver were also detected at doses ≥ 2 mg/kg in the 1-month study. Aminotransferase increases without single-cell necrosis were evident in the 6-month study; systemic exposures (AUC) to lomitapide in this study were higher than those at the threshold dose for such changes in the 1-month study. Because abetalipoproteinaemic patients have elevated aminotransferase levels, such increases in dogs may be related to downstream effects of MTP inhibition.

In a 1-year oral study in dogs at doses of 0.05, 0.5, and 5 mg/kg, lipid vacuolation in the small intestine, but not in the liver, was observed at doses ≥ 0.5 mg/kg, whereas decreases in serum cholesterol and/or triglycerides were seen at all doses. There were no important changes in serum transaminase levels in this study.

Interestingly, pulmonary histiocytosis observed in the 6-month rat study did not occur in any of the dog studies. Based on the available data, the lung concentrations of lomitapide and metabolites in dogs receiving 10 mg/kg were higher than those recorded in rats at 0.2 mg/kg (i.e., the threshold dose for pulmonary histiocytosis). This suggests that pulmonary histiocytosis is a species-specific finding in rats.

Hepatic effects

Hepatic effects are discussed as an important identified risk in this RMP and are addressed in all relevant sections of the Summary of Product Characteristics (SmPC).

Consistent with the mechanism of action of lomitapide, most treated patients exhibited increases in hepatic fat content. In an open-label Phase 3 study in adults, 18 of 23 patients with HoFH developed hepatic steatosis (hepatic fat >5.56%) as measured by nuclear magnetic resonance (NMR) spectroscopy. The median absolute increase in hepatic fat was 6% after both 26 weeks and 78 weeks of treatment, from 1% at baseline, measured by NMR spectroscopy. In an open-label Phase 3 study in paediatric patients, the median absolute increase in hepatic fat was 4.4% and 3.6% after 24 weeks and 104 weeks respectively, from 3.3% at baseline, measured by NMR imaging. 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 lomitapide, but whether histological sequelae remain is unknown, especially after long-term use.

Pulmonary histiocytosis

Based on the findings in rats, pulmonary function tests were included in most clinical trials. Actual values and changes over time were summarised for forced vital capacity (FVC), forced expiratory volume during 1 second (FEV_1), forced expiratory flow (25% - 75%) (FEF_{25-75}), and carbon monoxide lung diffusion (DLCO) parameters by treatment group. Lomitapide doses of up to 60 mg for a total treatment period of 78 weeks did not produce clinically significant changes in any pulmonary function parameters. In the APH-19 study, Pulmonary function test (PFT) were performed and changes from Baseline to Week 24, Week 56 and Week 104 were collected. There were no clinically meaningful changes from Baseline for any PFT assessment overall or in each age group. Furthermore, there were no TEAEs reported during the study that were related to a decrease in PFT results. Accordingly, no pulmonary safety concerns were raised.

The increased incidence of pulmonary histiocytosis in rats might be a direct consequence of the mechanism of action of lomitapide: since MTP expression in the lung is higher in rats than in humans and dogs, rats may be more susceptible to the accumulation of neutral lipid in alveolar macrophages than other species.

Reproductive/developmental toxicity

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 pregnant women were not included in clinical studies with lomitapide, the potential risk for humans is unknown. The SmPC reflects the non-clinical findings and contraindicates the use of lomitapide during pregnancy (Section 4.3 ‘Contraindications’). It also includes a section entitled ‘Contraception measures in women of childbearing potential’ in Section 4.4 ‘Special warnings and precaution for use’.

Use in pregnancy is important missing information in this RMP.

Genotoxicity

Toxicity in Juvenile Animals

A dose-finding study was conducted to aid dose selection for a definitive toxicity study in juvenile rats. Based on the results, 12 mg/kg/day was selected as the high dose in males and 3.5 mg/kg/day was selected as the high dose in females.

In the definitive study, juvenile rats received doses of 3, 6, and 12 mg/kg in males and 0.5, 1.5, and 3.5 mg/kg in females for 90 days with or without the addition of vitamin A, D, and E and essential fatty acids (Subsets A and B, respectively).

Exposures to lomitapide and its metabolites were consistently higher compared to a 1-month exposure, which suggested that the achievement of steady state is greater than 1 month in juvenile rats. Decreases in body weight parameters were observed for the majority of the dosing period.

Increased serum AST, ALT, and/or ALKP; increased incidences of hepatocellular findings; and delayed sexual maturation were observed in both subsets in both genders at all doses. Functional changes included decreases in hind limb grip strength in males at 12 mg/kg/day in Subset A and at ≥ 6 mg/kg/day in Subset B. There were no treatment-related effects on neurobehavioral parameters (i.e., locomotor activity; learning and memory; and auditory startle response) or long bone growth. In general, the effects on Subset B were greater than those in Subset A, which suggests that fat soluble vitamin/essential fatty acid supplementation ameliorates some of the actions of lomitapide in juvenile rats.

The relevance of delayed sexual maturation and decreased grip strength for the human patient population (hyperlipidaemic) is uncertain, as the rats used in this study were normolipidemic prior to the initiation of dosing. Following the recovery period, most affected parameters were reversible or showed evidence of reversibility.

Carcinogenicity

Two-year carcinogenicity studies were conducted in mice and rats. In mice, lomitapide was administered daily in the diet at doses of 0.3, 1.5, 7.5, 15 and 45 mg/kg/day. Rats received lomitapide by gavage at doses of 0.25, 1.7, and 7.5 mg/kg (males) and 0.03, 0.35, and 2.0 mg/kg (females).

In mice, the incidence of hepatocellular tumours (common in the strain tested, particularly in males) was significantly increased in a non-dose-related manner in males given lomitapide at ≥ 1.5 mg/kg and females given ≥ 7.5 mg/kg. Small intestinal tumours (rare in mice) were observed in a non-dose-related manner at all doses in males and at ≥ 15 mg/kg in females; however, statistical significance was achieved only in males given lomitapide at ≥ 15 mg/kg and females given 15 mg/kg. The no-effect doses for these tumours were 0.3 mg/kg in males and 1.5 mg/kg in females (liver) and < 0.3 mg/kg in males and 7.5 mg/kg in females (small intestine). Compared to the mean steady-state systemic exposure in humans at 60 mg, exposure multiples at the no-effect doses are estimated to be < 1 (males) and 2 (females) for liver tumours; for intestinal tumours, these multiples are estimated to be < 1 (males) and 9 (females).

Unlike mice, there were no statistically significant increases in tumour incidence in rats. This includes an increased incidence of pancreatic acinar cell adenoma observed in high-dose males at an exposure 6 times that in humans at 60 mg.

Although the relevance of the rodent tumours for humans is unknown, the following should be considered when evaluating tumour risk in HoFH patients treated with lomitapide:

- The tumours were not secondary to genotoxicity, and, based on the results of the repeat-dose toxicity and carcinogenicity studies do not appear to be secondary to immunotoxicity, steroid hormonal activity, or long-term tissue damage; thus, lomitapide is unlikely to present a carcinogenic hazard for humans at therapeutic doses/concentrations (Monro, 1998 *Drug Saf*).
- In mice, significant increases in liver and small intestine tumours mostly occurred at lomitapide doses associated with moderate to marked reductions in the levels of vitamins A and E in the liver compared to controls. As vitamins A and E are important free radical scavengers, a hypovitaminosis condition may have made these animals more susceptible to tumour induction.

- Based on the results of pharmacology studies with lomitapide in rodents, dogs, and monkeys, it is likely that the normolipidaemic mice and rats tested in the carcinogenicity studies had substantial reductions in lipid levels, which may have disturbed organ/tissue homeostasis. Furthermore, most tumours observed in mice occurred at ≥ 64 weeks of exposure. Compared to the average human lifespan of 78 years (Xu, 2010 Natl Vital Stat Rep), and assuming a 2-year lifespan in CD-1 mice, daily dosing in a mouse for 64 weeks is equivalent to approximately 50 years of daily dosing in humans.
- Following review of data from hundreds of pharmaceuticals registered in the 3 regions participating to the International Conference on Harmonisation (ICH), it was concluded that bioassay data from mice rarely contributed information that had any bearing on carcinogenic risk assessment in humans (Monro, 1998 *Drug Saf*). For instance, most of the approved statins (including atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin), produced positive carcinogenicity findings in studies in 2 animal species (MacDonald, 2004 *Toxicol Pathol;* Snyder, 2009 Environ Mol Mutagen) but, following extensive post-marketing experience, have not been associated with increased risk of cancer in humans.

From these data, however, it is not possible to state unequivocally that the tumour findings in rodents do not pose any risk to humans. Primary hepatic tumours, small intestinal tumours and pancreatic tumours are discussed as important potential risks in this RMP.

Safety pharmacology

The core battery of GLP safety pharmacology studies (as described in ICH S7A) was not conducted with lomitapide. Aegerion (a former MAH) conducted GLP CNS and hERG safety pharmacology studies; the latter studies were conducted in accordance with appropriate ICH guidelines (ICH S7A and S7B).

The lack of GLP respiratory and cardiovascular (in vivo) pharmacology studies with lomitapide did not appear to be important from a safety perspective as there were no safety alerts for these organ systems in clinical trials. It should be noted that pulmonary function tests were included in clinical studies as was electrocardiogram (ECG) monitoring.

Cardiovascular system, including potential effect on the QT interval

In a hERG assay, IC50 values for potassium channel current inhibition for lomitapide and the metabolites M1 and M3 were 1.7, 135, and > 300 µM, respectively. Compared to the predicted Cmax value in humans at 60 mg, these values are ≥ 220× higher. In rats given a single oral dose of lomitapide at 150 mg/kg, a mild decrease in heart rate was observed. In dogs given a single intravenous dose of lomitapide at 20 mg/kg, decreased blood pressure, heart rate and femoral arterial blood flow as well as an increase in T-wave amplitude on electrocardiograms were observed; 4 mg/kg was a no-effect dose. Although systemic exposures to lomitapide were not determined in the in vivo studies, they are likely to be much higher than in humans at 60 mg based on exposure data from repeat-dose studies in rats and dogs.

In a 1-month repeat dose toxicology study in dogs, minimal to moderate decreases in blood pressure and heart rate were observed at 2 and 20 mg/kg/d, which resulted in exposures that were approximately 37- and 230-times higher than at the maximum recommended human dose (MRHD) of 60 mg; in that study cardiovascular effects were not observed in dogs at clinically relevant doses.

The results of general and safety pharmacology testing suggest that undesirable cardiovascular effects are unlikely in humans at recommended doses of lomitapide. This has been borne out in clinical trials. Further, there were no cardiovascular safety signals in clinical trials with lomitapide.

Nervous system

In mouse and rat CNS studies with single oral doses of lomitapide up to 100 mg/kg, no behavioural effects were observed except for dose-related transient reductions in locomotor activity (≥ 10 mg/kg) and number of writhing to stimuli (≥ 30 mg/kg) in mice. Lomitapide was well tolerated in CNS tests in rats at 150 mg/kg. Although systemic exposures to lomitapide were not determined in these studies, they are likely to be much higher than in humans at 60 mg based on exposure data from repeat-dose studies in rodents.

These results suggest that undesirable pharmacologic activity related to the central nervous system is unlikely in humans at recommended doses of lomitapide.

Other toxicity-related information or data

Mechanisms for Drug Interactions

Non-clinical pharmacodynamic and pharmacokinetic studies were not performed in animals as it was considered more appropriate to obtain such data in humans.

Conclusions on non-clinical data

SAFETY CONCERNS	
Important identified risks (confirmed by clinical data)	Hepatic effects
Important potential risks (not refuted by clinical data or which are of unknown significance)	Primary hepatic tumours, small intestinal tumours, pancreatic tumours
Missing information	Use in pregnancy

PART II MODULE SIII - CLINICAL TRIAL EXPOSURE

Brief overview of development

During the lifecycle of lomitapide within this RMP, based on the results of the Phase 3 study in the paediatric population with HoFH (APH-19), the proposed label revision will extend the currently approved indication to include paediatric patients aged 5 years and older with HoFH as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without LDL apheresis. The paediatric development program also includes the introduction of a 2 mg dose (in the same hard capsule size as the adult dosage) to facilitate a lower starting dose for younger patients. The route of administration has not changed.

Clinical Trial Exposure

At the time of the MAA, a total of 29 studies were conducted with lomitapide, including Phase 1, 2, and 3 studies conducted in healthy adults, adults with HoFH, adults (without HoFH) with elevated LDL cholesterol (LDL-C) levels, adults with hepatic impairment, and adults with end-stage renal disease on dialysis. One study has been conducted with lomitapide in paediatric subjects aged 5 years and older with HoFH. Exposure data in subjects with HoFH (the sought indication) in adult and paediatric subjects and in all other clinical trial populations are shown below.

Paediatric population with Homozygous Familial Hypercholesterolaemia (HoFH)

A total of 43 male and female subjects between 5 and 17 years of age (mean age of 10.7 years) were treated in study APH-19, comprising 20 subjects aged 5 to 10 years, and 23 subjects aged 11 to 17 years. The majority (97.7%) of subjects were White and 1 subject (2.3%) was Black or African American. . Overall, mean (SD) and median weights at Baseline were 41.68 (18.505) and 43.30 kg, respectively (range: 15.8 to 78.0 kg). Mean (SD) and median BMI were 18.85 (5.071) and 18.90 kg/m^2, respectively (range: 11.2 to 32.6 kg/m^2).

In the 5 to 10 years age group (20 subjects), mean (SD) and median weights at Baseline were 26.11 (9.547) and 24.00 kg, respectively (range: 15.8 to 56.0 kg). Mean (SD) and median BMI were 15.78 (3.338) and 14.90 kg/m^2, respectively (range: 12.5 to 27.4 kg/m^2).

In the 11 to 17 years age group (23 subjects), mean (SD) and median weights at Baseline were 55.22 (12.758) and 55.00 kg, respectively (range: 21.9 to 78.0 kg). Mean (SD) and median BMI were 21.52 (4.840) and 20.70 kg/m^2, respectively (range: 11.2 to 32.6 kg/m^2). The demographic characteristic of APH-19 study is presented in Table 2.

Table 2 Demographic and other baseline characteristics of paediatric subjects in APH-19 study

	5 to 10 years N=20	11 to 17 years N=23	Overall N=43
Sex, n (%)			
Male	10 (50.0)	9 (39.1)	19 (44.2)
Female	10 (50.0)	14 (60.9)	24 (55.8)
Age, years			
Mean (SD)	7.0 (1.54)	14.0 (1.97)	10.7 (3.99)
Median	7.0	14.0	11.0
Range	5 to 10	11 to 17	5 to 17
Race, n (%)			
White	19 (95.0)	23 (100.0)	42 (97.7)
Black or African American	1 (5.0)	0	1 (2.3)
Ethnicity, n (%)			
Hispanic or Latino	1 (5.0)	0	1 (2.3)
Not Hispanic or Latino	19 (95.0)	23 (100.0)	42 (97.7)
Country, n (%)			
Germany	1 (5.0)	6 (26.1)	7 (16.3)
Spain	3 (15.0)	4 (17.4)	7 (16.3)
Italy	5 (25.0)	2 (8.7)	7 (16.3)
Saudi Arabia	3 (15.0)	10 (43.5)	13 (30.2)
Tunisia	5 (25.0)	1 (4.3)	6 (14.0)
Israel	3 (15.0)	0	3 (7.0)
Height at Baseline, cm			
Mean (SD)	126.89 (11.753)	159.98 (8.672)	144.59 (19.517)
Median	127.25	161.00	146.00
Range	107.8 to 144.0	140.0 to 177.0	107.8 to 177.0
Height percentile[a]			
Mean (SD)	64.287 (19.8167)	42.565 (27.2496)	52.668 (26.2064)
Median	58.000	36.000	50.000
Range	31.00 to 99.00	1.00 to 96.00	1.00 to 99.00
Height z score[b]			
Mean (SD)	0.407 (0.7595)	-0.198 (0.9045)	0.083 (0.8847)
Median	0.275	-0.270	0.090
Range	-0.72 to 2.33	-2.01 to 1.79	-2.01 to 2.33
Weight at Baseline, kg			
Mean (SD)	26.11 (9.547)	55.22 (12.758)	41.68 (18.505)
Median	24.00	55.00	43.30
Range	15.8 to 56.0	21.9 to 78.0	15.8 to 78.0
Weight z score[b]	n=19		
Mean (SD)	0.077 (1.2812)	-	-
Median	-0.430	-	-
Range	-1.40 to 3.13	-	-
Body mass index at Baseline, kg/m^2			
Mean (SD)	15.78 (3.338)	21.52 (4.840)	18.85 (5.071)
Median	14.90	20.70	18.90
Range	12.5 to 27.4	11.2 to 32.6	11.2 to 32.6

	5 to 10 years N=20	11 to 17 years N=23	Overall N=43
Body mass index percentile[a]			
Mean (SD)	38.867 (34.3409)	62.191 (32.6468)	51.343 (35.0762)
Median	28.500	64.340	50.000
Range	1.00 to 99.0	0.10 to 99.00	0.10 to 99.00
Body mass index z-score[b]			
Mean (SD)	-0.311 (1.3881)	0.263 (1.7024)	-0.004 (1.5728)
Median	-0.445	0.390	-0.070
Range	-2.39 to 3.01	-4.71 to 2.51	-4.71 to 3.01

Abbreviations: BMI=body mass index; CDC=Centers for Disease Control and Prevention; N=number of subjects in the analysis set; n=number of subjects meeting the criterion; SD=standard deviation; WHO=World Health Organization.

[a] Percentiles calculated using either World Health Organization (WHO) growth reference indicators for children 5 to 19 years or Center for Disease Control (CDC) website (https://www.cdc.gov/healthyweight/bmi/calculator.html).

[b] z scores calculated using the WHO growth reference indicators for children 5 to 19 years. Weight-for-age z scores are not available for 11 to 17 years due to the lack of WHO growth reference indicators.

(%)=n/N×100. BMI=weight (kg)/height $(m)^2$.

In study APH-19, the dose was initiated at the recommended starting dose for the subject's age and escalated to the maximum dose applicable to their age (5 to 10 years, 11 to 15 years, 16 to 17 years). A new capsule of 2 mg once daily has been introduced for children aged 5 to 15 years as recommended starting dose. Of the 43 subjects in the study, 35 subjects reached the maximum tolerated dose for age group during the Efficacy Phase (19/20 subjects in the 5 to 10 years age group, 13/17 subjects in the 11 to 15 years age group, and 3/6 subjects in the 16/17 years age group).

The maximum tolerated dose was defined as the highest dose of lomitapide through Week 24 that had not resulted in tolerability or safety concerns, and required to achieve LDL-C goal. In the 5 to 10 years age group, the maximum allowable dose of 20 mg was the maximum tolerated dose for 19 (95.0%) subjects, while 1 (5.0%) subject had a maximum tolerated dose of 5 mg. During the Safety Phase, 6 (30.0%) subjects achieved a maximum dose of 30 mg (beyond the original maximum dose for the age group, as per protocol amendment, based upon an investigator request and sponsor approval). In the 11 to 17 years age group, the majority of subjects achieved a maximum tolerated dose of 40 mg (13 [56.5%] subjects), while 3 (13.0%) subjects had a maximum tolerated dose of 60 mg. Maximum allowed dose was higher for subjects aged 16 to 17 years at Screening; of the 6 subjects in this age range, 3 subjects reached an maximum tolerated dose of 60 mg however all had to down-titrate soon after reaching this dose. For subjects aged 11 to 15 years, the maximum dose was 40 mg, and 13 of the 17 subjects in this age range achieved this dose. Exposure to lomitapide based on treatment duration (overall and at maintenance dose), average daily dose, and number of doses is presented in Table 3 for the Efficacy Phase and the Safety Phase.

Table 3 Clinical trial exposure for Paediatric HoFH trial by treatment duration and dose

	Efficacy Phase			Safety Phase		
	5 to 10 years N=20	**11 to 17 years N=23**	**Overall N=43**	**5 to 10 years N=20**	**11 to 17 years N=21**	**Overall N=41**
Treatment duration (weeks)						
Mean (SD)	24.38 (0.887)	23.55 (4.136)	23.94 (3.080)	79.81 (1.246)	75.94 (13.706)	77.83 (9.925)
Median	24.00	24.29	24.00	80.07	80.00	80.00
Range	23.6 to 27.0	10.9 to 27.1	10.9 to 27.1	76.6 to 82.1	25.1 to 85.9	25.1 to 85.9
Exposure to maintenance dose (weeks)						
Mean (SD)	9.09 (1.683)	8.62 (2.443)	8.84 (2.112)	69.46 (14.187)	69.51 (19.199)	69.49 (16.730)
Median	8	8	8	77.36	79.57	78.14
Range	7.7 to 13	6 to 16	6 to 16	31 to 81	17 to 85.9	17 to 85.9
Average daily dose (mg/day)						
Mean (SD)	8.77 (1.993)	17.87 (7.452)	13.64 (7.208)	19.48 (4.866)	33.27 (10.332)	26.54 (10.645)
Median	9.73	16.74	9.88	20.00	40.00	21.62
Range	1.9 to 11.0	4.5 to 33.1	1.9 to 33.1	4.7 to 26.5	9.7 to 51.7	4.7 to 51.7
Number of doses received						
Mean (SD)	168.2 (13.13)	164.9 (28.95)	166.4 (22.80)	553.6 (17.46)	531.6 (95.94)	542.3 (69.8)
Median	168.0	170.0	168.0	559.0	560.0	560.0
Range	119 to 189	76 to 190	76 to 190	488 to 568	176 to 601	176 to 601
Maximum tolerated dose, n (%)						
5 mg	1 (5.0)	1 (4.3)	2 (4.7)	1 (5.0)	0	1 (2.4)
10 mg	0	2 (8.7)	2 (4.7)	0	1 (4.8)	1 (2.4)
20 mg [a]	19 (95.0)	3 (13.0)	22 (51.2)	13 (65.0)	3 (14.3)	16 (39.0)
30 mg	0	1 (4.3)	1 (2.3)	6 (30.0)[b]	1 (4.8)	7 (17.1)
40 mg [c]	0	13 (56.5)	13 (30.2)	0	13 (61.9)	13 (31.7)
60 mg [d]	0	3 (13.0)	3 (7.0)	0	3 (14.3)	3 (7.3)

Abbreviations: N=number of subjects entering the respective phase and included in the analysis set.; n=number of subjects meeting the criterion; SD=standard deviation.
[a] Maximum allowed dose for subjects aged 5 to 10 years at Screening. Overall, 19 of the 20 subjects in this age range reached the maximum dose during the Efficacy Phase.
[b] Subjects were allowed to increase beyond 20 mg following a protocol amendment at the request of the investigator and sponsor approval.
[c] Maximum allowed dose for subjects aged 11 to 15 years at Screening. Overall, 13 of the 17 subjects in this age range reached the maximum dose during the Efficacy Phase.
[d] Maximum allowed dose for subjects aged 16 to 17 years at Screening. Overall, 3 of the 6 subjects in this age range reached the maximum dose during the Efficacy Phase.
(%)=n/N×100.

Adult patients with Homozygous Familial Hypercholesterolaemia (HoFH)

At the time of the MAA, the safety population for the HoFH study pool included a total of 35 subjects treated with lomitapide. Six subjects in this study pool were treated in Study UP1001 and 29 subjects were treated in Study UP1002/AEGR-733-005; 4 patients were common to both studies. Due to the rarity of the HoFH condition, the studies had a single-arm design to maximise the exposure database with lomitapide. A dose-escalation regimen of lomitapide was employed in both studies.

Subjects in Study UP1001 received escalated doses of lomitapide from 0.03 to 1.0 mg/kg/day. This Phase 2 single-arm trial was designed to evaluate the efficacy and safety of lomitapide in the treatment of subjects with HoFH. All 6 treated subjects completed the study, receiving 16 weeks of treatment with lomitapide.

Phase 3 Study UP1002/AEGR-733-005 was designed to evaluate the safety and efficacy of lomitapide as defined by percent change in LDL-C and other lipid parameters compared to baseline after 26 weeks of treatment in combination with other lipid-lowering therapies in adult patients with HoFH. Patients were then maintained on their individualised dose of lomitapide for an additional 52 weeks (for a total of 78 weeks of treatment). All efficacy, safety, and tolerability parameters were monitored for this period to determine the effects of long-term treatment. Dosing was initiated at 5 mg/day for 2 weeks and then escalated to 10 mg/day for 4 weeks, followed by escalations to 20, 40, and 60 mg/day at 4-week intervals as tolerated.

All of the 35 subjects enrolled in studies UP1001 and UP1002/AEGR-733-005 were treated with lomitapide. There were 6 (17.1%) premature discontinuations of study medication, the reason being adverse events (AEs; n=4), withdrawal by subject (20 mg dose after 139 days of therapy) (n=1) and non-compliance with study drug (5 mg dose after 4 days of therapy) (n=1). All but 1 of the discontinuations due to AEs was related to a GI disorder. One subject discontinued because of abdominal pain, nausea, and diarrhoea (10 mg dose after 83 days of therapy), and 1 subject each discontinued because of diarrhoea (10 mg dose after 69 days of therapy), gastroenteritis (5 mg dose after 37 days of therapy), or headache (40 mg dose after 119 days of therapy). A tabular overview of exposure and demographic data for the two HoFH trials is provided in Table 4 and Table 5 below.

In the Phase 3 UP1002/AEGR-733-005 clinical trial, subgroup analyses were not conducted on demographic characteristics. In addition to the data outlined in Table 4 and below, mean and median body mass index (BMI) were 25.8 and 24.4 kg/m^2, respectively; BMI ranged from 19.3 to 41.3 kg/m^2 across all 29 patients in the Safety/ITT population. Weight ranged from 52 to 139 kg with mean and median weights of 73.5 and 66.3 kg, respectively. No clinically significant differences in gender, weight or BMI across the maximum tolerated dose groups were observed.

At baseline, 18/29 (62%) patients were receiving apheresis, and the mean number of apheresis procedures was 1.4 per 4-week period. There were no significant differences in LDL-C lowering effect for patients who did and did not undergo apheresis.

Although the Phase 2 trial UP1001 used a weight-based dosing regimen, a fixed dose escalation regimen was chosen for the Phase 3 trial, after review of available pharmacokinetic data indicating that indices of body size and/or body weight did not have an impact on variability in drug exposure (maximum concentration or AUC), suggesting that weight-adjusted dosing was not an added benefit to patients.

Table 4: Clinical Trial Exposure for Adult HoFH Trials by Dose and Duration

Exposure parameter	UP1001 (N=6) n (%)	Final Escalated Dose Level at Week 26, UP1002/AEGR-733-005					
		5 mg (N=3) n (%)	10 mg (N=2) n (%)	20 mg (N=6) n (%)	40 mg (N=7) n (%)	60 mg[1] (N=11) n (%)	Total (N=29) n (%)
Total Dose (mg), n	6	3	2	5	7	11	28
Mean (SD)	2784.5 (667.63)	1018.3 (1601.02)	902.5 (555.08)	13919.0 (8109.75)	29578.6 (13851.64)	37177.3 (17468.62)	24659.1 (18999.57)
Median	2490.7	170.0	902.5	14595.0	36430.0	32760.0	26555.0
Min, Max	2238, 3840	20, 2865	510, 1295	1375, 24090	925, 39825	10310, 68770	20, 68770
Duration of Rx (days), n	6	3	2	6	7	11	29
Mean (SD)	119.5 (15.11)	193.0 (299.23)	78.0 (7.07)	681.8 (329.50)	856.0 (345.66)	792.4 (262.66)	673.6 (374.15)
Median	114.5	37.0	78.0	747.5	962.0	736.0	736.0
Min, Max	112, 148	4, 538	73, 83	134, 1133	119, 1122	493, 1274	4, 1274
Duration of Rx (days), n (%)							
1-30	0	1 (33.3)	0	0	0	0	1 (3.4)
31-91	0	1 (33.3)	2 (100)	0	0	0	3 (10.3)
92-182	0	0	0	1 (16.7)	1 (14.3)	0	2 (6.9)
183-365	6 (100.0)	0	0	0	0	0	0
366-545	0	1 (33.3)	0	1 (16.7)	0	2 (18.2)	4 (13.8)
546-730	0	0	0	1 (16.7)	0	3 (27.3)	4 (13.8)
731-1096	0	0	0	2 (33.3)	4 (57.1)	4 (36.4)	10 (34.5)
1097-1461	0	0	0	1 (16.7)	2 (28.6)	2 (18.2)	5 (17.2)

[1] Includes 1 subject whose final escalated dose level was 80 mg

Table 5: Clinical Trial Exposure for Adult HoFH Trials by Sex, Age, and Race

Characteristic	UP1001 (N=6) n (%)	Final Escalated Dose Level at Week 26, UP1002/AEGR-733-005					
		5 mg (N=3) n (%)	10 mg (N=2) n (%)	20 mg (N=6) n (%)	40 mg (N=7) n (%)	60 mg[1] (N=11) n (%)	Total (N=29) n (%)
Sex, n (%)							
Male	3 (50.0)	2 (66.7)	2 (100.0)	1 (16.7)	5 (71.4)	6 (54.5)	16 (55.2)
Female	3 (50.0)	1 (33.3)	0	5 (83.3)	2 (28.6)	5 (45.5)	13 (44.8)
Age (years), n	6	3	2	6	7	11	29
Mean (SD)	25.0 (9.19)	34.3 (11.59)	31.5 (12.02)	29.5 (8.73)	36.7 (13.57)	26.4 (8.44)	30.7 (10.56)
Median	21.0	36.0	31.5	27.5	33.0	22.0	30.0
Min, Max	17, 39	22, 45	23, 40	21, 41	19, 55	18, 44	18, 55
Race, n (%)							

Caucasian	3 (50.0)	3 (100.0)	2 (100.0)	5 (83.3)	4 (57.1)	11 (100.0)	25 (86.2)
Non-Caucasian	3 (50.0)	0	0	1 (16.7)	3 (42.9)	0	4 (13.8)

[1] Includes 1 subject whose final escalated dose level was 80 mg

All other Clinical Trial Populations

The safety population for the Elevated LDL-C and Other Risk Factors study pool included a total of 482 subjects treated with lomitapide, 78 subjects treated with an active control, and 116 subjects who received placebo. Subjects who received lomitapide in this study pool were classified into 1 of 4 dose groups, including an escalated dose group (2.5-5 mg or 5-10 mg, n=77), a low-dose group (2.5-7.5 mg, n=244), a mid-dose group (10 mg, n=99), and a high dose group (25-100 mg, n=62).

Subjects in this study pool were to receive study treatment for a duration ranging from 2 weeks to 12 weeks. The proportion of subjects who prematurely discontinued study medication was higher in the lomitapide groups (137 of 482 subjects, 28%) compared with the placebo (6%) and active control (9%) groups. Across the lomitapide dose groups, 19% of subjects in the escalated-dose group, 23% of subjects in the low-dose group, 48% of subjects in the mid-dose group, and 31% of subjects in the high-dose group prematurely discontinued study medication. The lower discontinuation rate in the 25 to 100 mg high-dose group of 31% compared with the 10 mg mid-dose group (48%) is likely related to the study designs; the studies that included the 25 to 100 mg doses were of shorter duration (2 to 4 weeks) compared with the 10 mg dose, which also included studies of 8 to 12 weeks in duration. Importantly, the lowest discontinuation rate for the lomitapide dose groups was observed in subjects who received escalated doses.

The safety population for the Single-dose Study Pool includes a total of 71 subjects treated with lomitapide and 26 subjects who received placebo. Subjects treated with lomitapide in this study pool were classified into 1 of 5 dose groups, including a 1 to 25 mg dose group (n=18), a 50 mg dose group (n=12), a 50 mg oral solution dose group (n=12), a 60 mg dose group (n=16), and a ≥100 mg dose group (n=13). In all groups other than the 50 mg oral solution dose group, subjects received lomitapide capsules. All enrolled subjects received their single dose of study medication. However, 1 subject prematurely discontinued participation in the study because of AEs (decreased consciousness, presyncope, dizziness, pallor, nausea, and headache).

A total of 241 subjects were treated in the Multiple-Dose Drug-Drug Interaction (DDI) or Crossover Studies. All but 12 (5%) subjects in this study pool completed their respective studies. Four (2%) subjects discontinued because of AEs, including 2 who discontinued because of AEs that occurred prior to receiving lomitapide. Other reasons for discontinuation included withdrawal of consent (6 subjects; 2%), Investigator decision (1 subject; <1%), and early termination of study by Sponsor (1 subject; <1%).

A tabular overview of exposure and demographic data for these study pools is provided in Table 6 and Table 7.

Table 6: Clinical Trial Exposure for Elevated LDL-C Pool, Single-Dose Pool, and Multiple-Dose DDI and Crossover Study Pool by Dose and Duration

DOSE OF EXPOSURE	DURATION OF TREATMENT (DAYS)	SUBJECTS N (%)
ELEVATED LDL CHOLESTEROL AND OTHER RISK FACTORS STUDY POOL		
Escalated (5-10 mg)	Mean (SD): 67.1 (22.77)	Total subjects: 77
	1-28 Days	7 (9.1)
	29-56 Days	14 (18.2)
	57-84 Days	46 (59.7)
	>84 Days	10 (13.0)
Low dose (2.5-7.5 mg)	Mean (SD): 66.5 (26.46)	Total subjects: 244
	1-28 Days	34 (13.9)
	29-56 Days	40 (16.4)
	57-84 Days	129 (52.9)
	>84 Days	41 (16.8)
Mid dose (10 mg)	Mean (SD): 39.2 (31.04)	Total subjects: 99
	1-28 Days	46 (46.5)
	29-56 Days	24 (24.2)
	57-84 Days	21 (21.2)
	>84 Days	8 (8.1)
High dose (25-100 mg)	Mean (SD): 20.2 (10.75)	Total subjects: 62
	1-28 Days	45 (72.6)
	29-56 Days	17 (27.4)
	57-84 Days	0
	>84 Days	0
SINGLE-DOSE STUDY POOL		
1-25 mg	1	18
50 mg	1	12
50 mg oral solution	1	12
60 mg	1	16
≥ 100 mg	1	13
MULTIPLE-DOSE DRUG-DRUG INTERACTION AND CROSSOVER STUDIES		
10 mg	[a]	80
50 mg	[a]	52
60 mg	[a]	109

[a] Duration of treatment is not presented here because of the crossover design and non-consecutive lomitapide dosing days in some of the studies in this pool.

Table 7: Clinical Trial Exposure for Elevated LDL-C Pool and Single-Dose Pools by Sex, Age, and Race

CHARACTERISTIC	ESCALATED (5-10 MG) (N = 77)	LOW DOSE (2.5-7.5 MG) (N = 244)	MID DOSE (10 MG) (N = 99)	HIGH DOSE (25-100 MG) (N = 62)
ELEVATED LDL CHOLESTEROL AND OTHER RISK FACTORS STUDY POOL				
Sex, n (%)				
Male	39 (50.6)	121 (49.6)	41 (41.4)	42 (67.7)
Female	38 (49.4)	123 (50.4)	58 (58.6)	20 (32.3)

CHARACTERISTIC	ESCALATED (5-10 MG) (N = 77)	LOW DOSE (2.5-7.5 MG) (N = 244)	MID DOSE (10 MG) (N = 99)	HIGH DOSE (25-100 MG) (N = 62)
Age (years), n	77	244	99	62
Mean (SD)	56.6 (6.96)	52.0 (10.80)	51.8 (11.62)	46.2 (10.60)
Median	57.0	54.0	53.0	46.0
Min, Max	40, 71	20, 70	21, 70	26, 65
Age Category, n (%)				
18-64	68 (88.3)	216 (88.5)	82 (82.8)	61 (98.4)
≥65	9 (11.7)	28 (11.5)	17 (17.2)	1 (1.6)
Race, n (%)				
Caucasian	60 (77.9)	177 (72.5)	71 (71.7)	42 (67.7)
Non-Caucasian	17 (22.1)	67 (27.5)	28 (28.3)	20 (32.3)
SINGLE-DOSE STUDY POOL				
Sex, n (%)				
Male	18 (100.0)	12 (100.0)	12 (100.0)	12 (75.0)	13 (100.0)
Female	0	0	0	4 (25.0)	0
Age (years), n	18	12	12	16	13
Mean (SD)	33.8 (5.34)	35.3 (7.05)	28.6 (7.25)	51.4 (4.69)	38.3 (8.05)
Median	33.0	36.0	27.0	52.0	38.0
Min, Max	24, 41	25, 45	21, 45	41, 58	25, 50
Race, n (%)					
Caucasian	9 (50.0)	5 (41.7)	9 (75.0)	12 (75.0)	6 (46.2)
Non-Caucasian	9 (50.0)	7 (58.3)	3 (25.0)	4 (25.0)	7 (53.8)

A brief review of the demographic characteristics for the 6 studies included in the Multiple-Dose DDI and Crossover Studies pool is provided below, by study.

AEGR-733-002: Of the 129 subjects who entered the study, 76 were male and 53 were female ranging in age from 18 to 57 years. Eighty-two of the subjects were Caucasian, 23 were Black, 15 were Asian, and the remaining 9 subjects were of other/mixed race. BMI ranged from 18.4 to 30.0 kg/m^2.

AEGR-733-013: All 16 subjects were healthy males ranging in age from 20 to 55 years. Twelve subjects were Caucasian and 4 were Black. BMI ranged between 21.4 and 28.3 kg/m^2.

AEGR-733-015: All 27 subjects were healthy females ranging in age from 23 to 40 years. Twenty subjects were Caucasian, 6 were Black, and 1 was Asian. BMI ranged between 19.2 and 29.9 kg/m^2.

AEGR-733-018: Of the 30 subjects who entered the study, 24 were male and 6 were female ranging in age from 24 to 53 years. Nineteen subjects were Caucasian, 9 were Black, and 2 were Asian. BMI ranged between 20.7 and 29.6 kg/m^2.

AEGR-733-019: Of the 16 subjects who entered the study, 13 were male and 3 were female. Twelve subjects were Caucasian, 3 were Black, and 1 was Asian. Subjects ranged in age from 24 to 47 years, inclusive, and had a BMI between 20.3 and 29.6 kg/m^2, inclusive. (CSR AEGR-733-019, Table 14.1-2)

CV145-005: Of the 25 subjects who entered the study, 16 were male and 9 were female ranging in age from 19 to 54 years. Twenty-four subjects were Caucasian and 1 was Black. BMI was not reported. (CSR CV145-005, Table 8.3.1)

Further, 9 studies have been conducted to date that are not included in the above-mentioned study pools. These studies were not pooled, either because the designs or patient groups did not allow for appropriate pooling, or because they were conducted post-approval. The 9 studies are as follows:

Table 8: Additional Adult Clinical Studies Non-Pooled.

STUDY NUMBER	STUDY TYPE	POPULATION	NUMBER OF SUBJECTS
Pre-Approval			
AEGR-733-011	Thorough QT study	Healthy volunteers	56
AEGR-733-003a[1]	R, DB, placebo-controlled efficacy and safety study	Subjects between 51 and 61 years of age with Frederickson Type IIa or IIb dyslipidemia	113
AEGR-733-021	P1, open-label, parallel group safety and PK study	Subjects between 18 and 65 years of age with ESRD who were on haemodialysis and matched controls	14 (7 per group)
Post-Approval			
AEGR-733-023	P1, PK/PD in Japanese versus Caucasian subjects	Male subjects between 20 and 45 years of age with elevated LDL-C	36 Japanese; 36 Caucasian
AEGR-733-026	P1, open-label, crossover, intra-subject variability, PK	Healthy volunteers	15
AEGR-733-032	P1,open label, randomized, crossover, bioavailability	Healthy volunteers	32
AEGR-733-024	P1 DDI with atorvastatin	Healthy volunteers	32
AEGR-733-029	P1 DDI with OC	Healthy female volunteers	32
AEGR-733-012	P3 open-label extension study	HoFH	19 subjects from the P3 study (UP1002/AEGR-733-005)

[1] This study was discontinued by the Sponsor because of an unexpected high rate and severity of GI symptoms with GI events occurring sooner on treatment than had been previously observed; no subject completed the full 8 weeks of treatment. After the study was discontinued, an investigation suggested that microbial contamination (*Bacillus cereus*) may have occurred in the capsule used to prepare the drug product for this study. The GI symptoms observed in this study were consistent with the GI symptoms associated with *B. cereus* infection and the contamination may have augmented the rate and severity of GI AEs experienced by the subjects receiving lomitapide alone or coadministered with atorvastatin.

Study Reports with Implications for Safety Concerns

Two non-clinical studies have been performed in juvenile rats. Neither of these studies had any implications for safety concerns for adults. The results of these studies (AEGR 733PC0030 and AEGR 733PC0031) are summarised in Module SII. However, the applicant received the following comment from EMA following of the submission of these non-clinical study results:

"Data from the carcinogenicity study (in the original submission) indicate an association between the occurrence of pancreas acinar cell hyperplasia or adenoma on the one hand and reduced zymogen on the other hand and the data from the juvenile toxicity studies suggest that juvenile rats may be more sensitive to this effect than adult rats. Currently there is no application for a paediatric indication. In a potential future application for a paediatric indication, it should be addressed whether such a mechanism may be relevant for humans. There should be sufficient certainty that the earlier occurrence of reduced zymogen in juvenile rats compared to adult rats is not a marker for an increased risk of pancreatic cancer. If such a mechanism would be valid, the increased demand for lipase is expected to lead to increased secretion of lipase, which can be measured in the clinic. We recommend therefore monitoring in clinical studies in children / adolescents whether lomitapide leads to an enhanced secretion of lipase compared to adults."

In the APH-19 study, serum lipase was measured at Baseline, Week 24, Week 56, and at Week 104, and no clinically significant serum lipase levels were observed.

In addition, sexual maturation was assessed in APH-19 based on Tanner Staging and on either serum testosterone (males) or serum oestradiol (females) in subjects who were Tanner Stage ≥2. Sex hormones were assessed at Baseline, Week 56, and Week 104. A total of 14 subjects were assessed for oestradiol and 8 subjects were assessed for testosterone in the 11 to 17 years age group and no clinically significant deviations from normal for oestradiol or testosterone were reported during the study; increases in oestradiol and testosterone were within expected developmental ranges.

Two drug-drug interaction studies have been performed to investigate the interaction of lomitapide with the weak CYP 3A4 inhibitor atorvastatin (AEGR-733-024) and with the weak CYP 3A4 inhibitor ethinyl estradiol (EE)/norgestimate (Ortho Cyclen) (AEGR-733-029). A summary of the results of these studies is presented below.

Additionally, updates to the physiologically based pharmacokinetic (PK) modelling and simulation of lomitapide exposure with co-administration of CYP3A4 inhibitors has been performed (AEGR 733PC0029, AEGR-733PC0035). The objective of this analysis was to predict the impact of CYP3A4 inhibitors on the concentration-time profile of lomitapide using a physiologically-based (PBPK) modelling and simulation approach that has been qualified by data from the interaction study with ketoconazole (AEGR-733-018) and updated based on new data from interaction studies with atorvastatin (AEGR-733-024) and EE/norgestimate (AEGR-733-029). To achieve this goal, a physiologically based PK model was developed. The developed and validated model was then used to predict the impact of weak, moderate, and strong CYP3A4 inhibitors on the PK of lomitapide. The simulations predict that both strong and moderate CYP3A4 inhibitors will have a substantial impact on the PK (mean AUC ratios >5) of lomitapide. These findings are in agreement with the clinical observation for ketoconazole, where a pronounced increase in the plasma exposure of lomitapide was determined following its co-administration. The updated simulation utilizing new data from interaction studies with atorvastatin and EE/norgestimate predicts that weak CYP3A4 inhibitors have a varying effect on the PK (mean AUC ratios 1-2) of lomitapide when the 2 therapies are taken together. The simulation predicts a minimal effect on lomitapide PK (mean AUC ratios 1-1.54) when lomitapide is taken 12 hours apart from a weak CYP3A4 inhibitor. These findings are in agreement with the results of the two DDI studies summarized below.

AEGR-733-024: A Phase 1, Open-Label, Randomized, 2-Arm Study to Evaluate the Effect of Atorvastatin, a Weak CYP3A4 Inhibitor, on the Pharmacokinetics of Lomitapide in Healthy Subjects

This was a Phase 1, open-label, randomized, 2-arm, 2-period drug interaction study in 32 healthy male and female subjects to evaluate the effects of steady-state atorvastatin on the PK of single-dose lomitapide when atorvastatin was administered at the same time as lomitapide or 12 hours after lomitapide.

Systemic exposure to lomitapide, as assessed by AUC and Cmax, was approximately 2-fold higher following simultaneous coadministration of lomitapide with atorvastatin compared to lomitapide alone. Systemic exposure to lomitapide was slightly increased (approximately 1.3-fold increase for both AUC and Cmax) following coadministration of lomitapide with atorvastatin 12 hours apart.

Lomitapide (20 mg) was well tolerated when administered alone or in combination with 80 mg atorvastatin simultaneously or 12 hours apart. A total of 17 subjects (53.1%) experienced a total of 40 treatment-emergent adverse events (TEAEs) during the study. Of those, a total of 30 TEAEs reported by 13 (40.6%) subjects were considered to be possibly related to lomitapide. None of the TEAEs were considered to be possibly related to atorvastatin. All TEAEs were mild in severity. No serious AEs were reported.

The incidence of AEs was higher following coadministration of lomitapide with atorvastatin simultaneously versus lomitapide alone (9 [56.3%] subjects and 2 [12.5%] subjects, respectively) with GI symptoms constituting the majority of the increase. One subject (6.3%) experienced a GI TEAE (toothache) on lomitapide alone while 8 subjects (50%) experienced a GI TEAE (diarrhoea, abdominal pain, nausea) when lomitapide was taken simultaneously with atorvastatin.

The incidence of AEs was similar following coadministration of lomitapide with atorvastatin 12 hours apart (3 [18.8%] subjects) compared to lomitapide alone (2 [12.5%] subjects) with similar rates of GI TEAEs (2 subjects [12.5%] for both).

Isolated occurrences of potentially clinically significant changes in seated systolic blood pressure (SBP; change from baseline >30 mmHg) and diastolic blood pressure (DBP; change from baseline >20 mmHg) were reported for 8 subjects. There were no clinically significant findings in laboratory assessments, ECGs, and physical examinations for this study.

AEGR-733-029: A Phase 1, Open-label, Randomized, 2-Arm Study to Evaluate the Effect of Ethinyl Estradiol/Norgestimate (Ortho Cyclen®), a Weak CYP3A4 Inhibitor, on the Pharmacokinetics of Lomitapide in Healthy Female Subjects

This single-centre, 2-arm, 2-period drug interaction study was conducted to evaluate the effects of EE/norgestimate (0.035 mg/0.25 mg), a weak CYP3A4 inhibitor, on the PK of lomitapide (20 mg) in healthy female subjects when EE/norgestimate was administered simultaneously with lomitapide and when administration was separated by 12 hours. Thirty-two female subjects were enrolled; 28 subjects were included in the PK analysis.

Systemic exposure to lomitapide, as assessed by AUC and Cmax, was slightly higher (approximately 1.4-fold and 1.3-fold increase, respectively) for simultaneous coadministration of lomitapide with EE/norgestimate compared to lomitapide alone. Systemic exposure to lomitapide was approximately 1.3-fold and 1.2-fold higher for AUC and Cmax, respectively, following coadministration of lomitapide with EE/norgestimate 12 hours apart.

A similar mean lomitapide t1/2 was observed for all treatment arms, values ranged from 51.0 to 53.6 hours.

Lomitapide was well tolerated when administered alone or in combination with EE/norgestimate. The incidence of AEs was similar between the 2 treatment arms. Three (18.8%) subjects experienced TEAEs on lomitapide alone in both Arm 1 and Arm 2. Four (25%) subjects experienced TEAEs when EE/norgestimate was taken simultaneously with lomitapide. Two (15.5%) subjects experienced TEAEs when EE/norgestimate was taken 12 hours apart from lomitapide. There were no reports of SAEs.

Potentially clinically significant changes in seated SBP (change from baseline >30 mmHg) and DBP (change from baseline >20 mmHg) were reported for some subjects. These individual subject changes were transient and were not related to TEAEs. There were no clinically significant findings in laboratory assessments, physical examinations, and ECGs for this study.

As a result of these study results, the SmPC (approved 30 Mar 2015 for the adult population) was revised to provide the following advice when lomitapide is taken with weak CYP 3A4 inhibitors:

Section 4.2: Posology and method of administration

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

- Separate the dose of the medications by 12 hours.

OR

- Decrease the dose of lomitapide by half. Adult patients on 5 mg should remain on 5 mg. Paediatric patients on 2 mg should remain on 2 mg.

Careful titration may then be considered according to LDL-C response and safety/tolerability. Upon discontinuation of atorvastatin the dose of lomitapide should be up-titrated according to LDL C response and safety/tolerability.

For patients on a stable maintenance dose of lomitapide who receive any other weak CYP3A4 inhibitor, separate the dose of the medications (lomitapide and the weak CYP3A4 inhibitor) by 12 hours. Exercise additional caution if administering more than 1 weak CYP3A4 inhibitor with lomitapide. Consider limiting the maximum dose of lomitapide according to desired LDL-C response.

Section 4.4: Special warnings and precautions for use

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 adult patient with HoFH developed markedly elevated aminotransferase (ALT 24× ULN, AST 13× 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. The dose of Lojuxta should be administered 12 hours apart from any other weak CYP3A4 inhibitor.

Section 4.5: Interaction with 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	Use of strong or moderate inhibitors of CYP3A4 is contraindicated with Lojuxta. If

MEDICINAL PRODUCTS	EFFECTS ON LOMITAPIDE LEVELS	RECOMMENDATION CONCERNING CO-ADMINISTRATION WITH LOJUXTA
	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 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. 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.	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. When administered with atorvastatin, the dose of lomitapide should either be taken 12 hours apart or be decreased by half (see section 4.2). The dose of lomitapide 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 drugs 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.

APH-19: A Single-arm, open-label, international, multi-centre study to evaluate the efficacy and safety of lomitapide in paediatric subjects aged 5 to 17 years of age, with HoFH on stable lipid-lowering therapy.

Overall, 41 of the 43 (95.3%) subjects treated with lomitapide in this study completed the Efficacy Phase (Week 24). Two subjects (siblings) discontinued prematurely due to moderate diarrhoea, despite being offered to continue in the study at a lower dose. A further two subjects discontinued during the Safety

Phase of the study (from Week 24 to Week 104). At the end of the study, the majority (35/39 subjects) of subjects continued receiving lomitapide either by transitioning to commercial product or enrolling in the EAP, indicating an acceptable safety and efficacy profile for the subject and their healthcare professional.

A 2 mg formulation of lomitapide capsule has been developed to facilitate initial dosing in younger children (aged 5 to 15 years).

During the pivotal paediatric study (APH-19), subjects were given the option to sprinkle the content of the capsule onto mashed banana or apple sauce. Only 3 subjects reported being unable to swallow the capsule at some timepoints; in such cases the capsule was opened and sprinkled on mashed banana puree. Palatability data collected indicate no problems with administration of lomitapide when swallowing the capsule.

The APH-19 study demonstrated that lomitapide as an adjunct to a low-fat diet and LLT (including LA) reduced LDL-C in paediatric subjects, 5 years and older with HoFH by clinically meaningful and statistically significant magnitudes that were confirmed across all sensitivity, supplementary, and subgroup analyses. The findings were consistent with those reported for adult subjects with HoFH.

The adverse events of special interest (AESIs) assigned were identical to those defined in the EU Risk Management Plan for Lomitapide for adults and are based on the principal site of action of lomitapide and important potential risks.

Treatment with lomitapide in paediatric subjects revealed no new safety signals compared to adult patients. The most frequently reported side effects were transient gastrointestinal disorders or hepatic abnormalities that resolved either with dose reduction/suspension or without any action taken. Gastrointestinal events were less frequent and less severe in paediatric patients. No clinically significant changes in serum oestradiol or testosterone were reported, and increases were within expected developmental ranges. Hepatic fat accumulation was mild and consistent with published evidence for adults. Growth and development of the children were not adversely impacted by treatment with lomitapide.

As a result of the study results, the SmPC was revised to provide the following guidance related to lomitapide use in the paediatric population.

Section 1: Name of the medicinal product

Lojuxta 2 mg hard capsules

Lojuxta 5 mg hard capsules

Lojuxta 10 mg hard capsules

Lojuxta 20 mg hard capsules

Section 2: Qualitative and quantitative composition

Lojuxta 2 mg hard capsules

Each hard capsule contains lomitapide mesylate equivalent to 2 mg lomitapide.

Excipient with known effect

Each hard capsule contains 148.89 mg lactose (as monohydrate)

Section 3: Pharmaceutical form

The capsule is a grey cap/grey body hard capsule of 19.4 mm, printed with black ink imprinted with

"2 mg" on body and "A733" on cap.

Section 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 for the treatment of adult and paediatric patients aged 5 years and older with homozygous familial hypercholesterolaemia (HoFH).

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

Section 4.2: Posology and method of administration

Paediatric patients (aged 5 to 10 years)

The recommended starting dose for children aged 5 to 10 years is 2 mg once daily. After 8 weeks the dose may be increased, according to LDL-C response and based on acceptable safety and tolerability, to 5 mg and then, at a minimum of 4-week intervals, to 10 mg and to the maximum recommended dose of 20 mg. The dose may be further increased to 30 mg, if safety and tolerability permit, after a minimum of 6 months from start of treatment.

Paediatric patients (aged 11 to 15 years)

The recommended starting dose for children aged 11 to 15 years is 2 mg once daily. After 4 weeks the dose may be increased, according to LDL-C response and based on acceptable safety and tolerability, to 5 mg and then, at a minimum of 4-week intervals, to 10 mg, 20 mg, and to the maximum recommended dose of 40 mg

Paediatric patients (aged 16 to 17 years)

The recommended starting dose for children aged 16 to 17 years is 5 mg once daily. After 4 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 and to the maximum recommended dose of 40 mg.

Adults and paediatric patients (aged 5 to 17 years)

The dose should be escalated gradually to minimise the incidence and severity of gastrointestinal adverse reactions and aminotransferase elevations. For paediatric patients, when a patient crosses over into the next age category, the dose of lomitapide can be escalated to the maximum recommended dose applicable for the new age category. It is recommended to exercise caution in paediatric patients who have a low body weight or height for their age (<15 kg or BMI and height <10th percentile according to WHO Growth Charts for Boys and Girls 5 to 19 Years of Age).

The occurrence and severity of gastrointestinal adverse reactions associated with the use of lomitapide 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.

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

- the dose of the medicinal products should be separated by 12 hours

OR

- the dose of lomitapide should be decreased by half. Adult patients on 5 mg should remain on 5 mg. Paediatric patients on 2 mg should remain on 2 mg.

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 for adults and children 9 years and older or 200 IU vitamin E for children aged 5 to 8 years, 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.

Special populations

Adult patients with mild hepatic impairment (Child-Pugh A) should not exceed 40 mg daily. Paediatric patients with mild hepatic impairment (Child-Pugh A) should not exceed the following daily doses of lomitapide: children aged 5 to 10 years should not exceed 10 mg daily; children aged 11 to 17 years should not exceed 20 mg daily.

Renal impairment

Adult patients with end stage renal disease receiving dialysis should not exceed 40 mg daily . Paediatric patients with end stage renal disease receiving dialysis should not exceed the following daily doses of lomitapide: children aged 5 to 10 years should not exceed 10 mg daily; children aged 11 to 17 years should not exceed 20 mg daily.

Paediatric population

The safety and efficacy of lomitapide in children aged less than 5 years have not yet been established. 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 with a glass of water, at least 2 hours after the evening meal because the fat content of a recent meal may adversely impact gastrointestinal tolerability. If the patient is unable to swallow the intact capsule(s), the capsule(s) can be opened and the contents sprinkled on a small amount (1 tablespoon) of apple sauce or banana puree, which are essentially fat free.

Section 4.4: Special warnings and precautions for use

Dose adjustment and monitoring for patients with elevated aminotransferases remains the same; however, the recommendations should be based on age and gender appropriate upper limits of normal (ULN).

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 in adults, 18 of 23 patients with HoFH developed hepatic steatosis (hepatic fat > 5.56%) as measured by nuclear magnetic resonance (NMR) spectroscopy. The median absolute increase in hepatic fat was 6% after both 26 weeks and 78 weeks of treatment, from 1% at baseline, measured by NMR spectroscopy. In an open-label Phase 3 study in paediatric patients, the median absolute increase in hepatic fat was 4.4% and 3.6% after 24 weeks and 104 weeks respectively, from 3.3% at baseline, measured by NMR imaging / magnetic resonance imaging (MRI). 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:

For paediatric patients:

- Imaging for hepatic fat content by ultrasound or NMR imaging / MRI.
- GammaGT and serum albumin to detect possible liver injury.

Contraception measures in women and adolescents of childbearing potential

Before initiating treatment in women and adolescents of childbearing 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. Oestrogen-containing oral contraceptives are weak CYP3A4 inhibitors.

Section 4.8: Undesirable effects

Following the paediatric study, no new adverse reactions were added.

Summary of Subject Disposition

Safety data integrated across studies up to the MAA are presented for the HoFH, Elevated LDL-C and Other Risk Factors, Single-Dose Study, and Multiple-Dose DDI and Crossover Studies Pools. Across these 4 primary study pools, a total of 1049 subjects were treated, including 829 who received lomitapide (as monotherapy or co-administered with other lipid-lowering therapies) and 220 who received placebo or active control drugs. Additionally, 43 subjects received lomitapide as being part of the paediatric APH-19 clinical study. A summary of subject disposition for these 1049 subjects is presented in Table 9, by study pool.

Thirty-five subjects with HoFH are included in the adult HoFH pool; all 35 were treated with lomitapide. A total of 676 subjects is included in the Elevated LDL-C and Other Risk Factors pool, of whom 482 were treated with lomitapide and 194 received either placebo or active control. A total of 97 subjects is included in the Single-Dose Study Pool, of whom 71 subjects received lomitapide and 26 subjects received placebo. A total of 241 subjects was treated in the Multiple-Dose DDI or Crossover Studies. A total of 43 subjects was included in the paediatric APH-19 study and all subjects with HoFH received lomitapide.

Table 9: Subject Disposition by Study Pool (Adults) and Paediatric HoFH Population

Disposition Parameter	Adult HoFH Indication	Paediatric HoFH Indication	Elevated LDL-C and Other Risk Factors	Single Dose Studies	Multiple-Dose DDI Crossover	Total
Received at least one dose of study medication	35	43	676	97	241	1092
Prematurely discontinued study medication	6 (17.1)	4 (9.3)	151 (22.3)	1 (1.0)	12 (5.0)	174 (15.9)
Adverse Event	4 (11.4)	2 (4.7)	128 (18.9)	1 (1.0)	4 (2.0)	139 (12.7)
Withdrawal by subject	1 (2.9)	1 (2.3)	14 (2.1)	0	6 (2.0)	22 (2.0)
Lost to follow-up	0	0	2 (0.3)	0	0	2 (0.2)
Non-compliance with study drug	1 (2.9)	0	0	0	0	1 (0.1)
Death	0	0	0	0	0	0
Other	0	1 (2.3)	7 (1.0)	0	2 (2.0)	10 (0.9)

Among all 1092 subjects across the 4 primary adult study pools and paediatric population, 918 (84.1%) completed the study and 174 (15.9%) discontinued study medication prematurely. The most common reason for study medication discontinuation was AE (139 subjects; 12.7%) with similar incidence observed in the adult HoFH and Elevated LDL-C and Other Risk Factors pools. Only 1 subject was reported as discontinued from the single-dose studies. Other reasons for discontinuation were reported for small proportions of subjects and included withdrawal of consent by subject (22 subjects; 2%), lost to follow-up (2 subjects; <1%), and non-compliance with study medication (1 subject; <1%). Additionally, 10 subjects (<1%) discontinued for “other” reasons.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in clinical studies within the development programme

History of biopsy-proven cirrhosis or abnormal liver function tests (LFTs)

Criteria

UP1002/AERG-733-005

History of biopsy-proven cirrhosis or abnormal liver function tests (LFTs) at screening (AST or ALT >2 x upper limit of normal and/or total bilirubin of >1.5 mg/dL (25.7 µmol/L) unless patient has unconjugated hyperbilirubinemia due to Gilbert's syndrome).

Documented diagnosis of any of the following liver diseases:

a) Non-alcoholic steatohepatitis (NASH)

b) Alcoholic liver disease

c) Autoimmune hepatitis

d) Primary biliary cirrhosis

e) Primary sclerosing cholangitis

f) Wilson's disease

g) Haemochromatosis

h) α1-antitrypsin deficiency

UP1001

History of liver disease or abnormal LFTs at Screening (>3x upper limit of normal)

Reason for exclusion:

Lomitapide is known to cause hepatic aminotransferase elevations and hepatic steatosis. Due to the risk that these effects may reflect or cause hepatocellular injury, patients with pre-existing liver disease (as defined in the clinical trial protocols) were excluded.

Is it considered to be included as missing information?

Yes.

Rationale

Lomitapide is contraindicated in patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests.

Known significant GI bowel disease or malabsorption such as inflammatory bowel disease or chronic pancreatitis requiring use of daily pancreatic enzymes.

Reason for exclusion:

These patients were excluded from clinical studies due to the known effect of lomitapide on absorption of triglyceride from the GI tract and the potential to cause malabsorption of fat-soluble nutrients.

Is it considered to be included as missing information?

No.

Rationale

Lomitapide is contraindicated in patients with a known significant or chronic bowel disease such as inflammatory bowel disease or malabsorption.

Pregnancy and patients with inadequate contraception.

Reason for exclusion:

Animal studies have shown developmental toxicity (teratogenicity and embryotoxicity). There is no reliable data on use in pregnant women and the potential risk to humans is unknown. Pregnant patients and patients without adequate contraception were excluded from clinical trials.

Is it considered to be included as missing information?

Yes.

Rationale

Pregnant or breast-feeding women were excluded from the clinical development programme. There is no reliable data on its use in pregnant women and hence the potential risk for humans is unknown. Because lomitapide may induce vomiting and diarrhoea, there is the possibility of reduced effectiveness of oral contraception.

Chronic hepatitis B & C as defined by positive for hepatitis B & C surface antigen (HBsAg & HepCAb).

Reason for exclusion:

These patients were excluded from clinical trials as lomitapide is known to have a hepatic effect and as these criteria were risk factors for hepatic disease, as a precautionary measure, such patients were excluded.

Is it considered to be included as missing information?

No.

Rationale

Whilst these patients are at risk of hepatic disease, they may not demonstrate active liver disease per se. However, such patients with risk factors for liver disease should only be prescribed lomitapide with caution and the SmPC provides extensive advice on regular liver function monitoring and screening.

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 Cmax were 164% and 361% higher, respectively, compared with healthy volunteers. In patients with mild hepatic impairment, lomitapide AUC and Cmax were 47% and 4% higher, respectively, compared with healthy volunteers. Accordingly, the SmPC states that ‘Patients with mild hepatic impairment (Child Pugh A) should not exceed 40 mg daily’.

History of alcohol or drug abuse

Criteria

Male subjects reporting more than 2 drinks per day or females reporting more than 1 drink per day (1 drink = 12 oz beer, 1 oz hard liquor, 5 oz wine; 1 oz = 29.6 mL).

Certain prohibited medications known to be potentially hepatotoxic, especially those that can induce microvesicular or macrovesicular steatosis. These included, but were not limited to, isotretinoin, amiodarone, heavy acetaminophen use (4 g/day >3 x every week), methotrexate, tetracyclines, and tamoxifen.

Reason for exclusion:

These patients were excluded from clinical trials as lomitapide is known to have a hepatic effect and as these criteria were risk factors for hepatic disease, as a precautionary measure, such patients were excluded.

Is it considered to be included as missing information?

No.

Rationale

The SmPC advises that the use of alcohol is not recommended, and that caution should be exercised if other hepatotoxic drugs are used concomitantly.

History of chronic renal insufficiency (serum creatinine >2.5 mg/dL).

Reason for exclusion:

Patients with chronic renal failure were excluded as a precaution based upon the observed increase in AUC and Cmax of 40% to 50%.

Is it considered to be included as missing information?

No.

Rationale

The SmPC states that 'Patients with end-stage renal disease receiving dialysis should not exceed 40 mg daily' and provides further information on this special population in Section 5.2 of the SmPC. Since clinical data in patients with renal failure are limited and the exposure–response relationship for lomitapide is not fully characterized with regard to safety, a conservative approach towards dosing in patients with end-stage renal disease on dialysis is reasonable based on the observed increase in exposure.

A pharmacokinetic study in patients with end-stage renal disease undergoing intermittent haemodialysis demonstrated increases of 34% to 40% in the geometric mean total exposures (AUC0-inf, AUC0-t, and AUC0-72) of lomitapide in subjects with end-stage renal disease (ESRD) on haemodialysis compared with normal healthy subjects. An increase of 51% was observed in the geometric mean Cmax of lomitapide in subjects with ESRD on haemodialysis compared with normal healthy subjects. Based on the pharmacology and disposition of lomitapide, the changes in lomitapide Cmax and AUC observed in subjects with ESRD relative to matched healthy controls were modest and demonstrated some variability. Although the differences observed crossed the pre-defined statistical criteria in the study protocol, these observations are not considered to be clinically important. The pharmacological activity of lomitapide is limited to the GI tract and liver, consistent with the indirect pharmacokinetic/pharmacodynamic model developed by Bristol-Myers Squibb in the rat model. As a result, the observed increase in AUC and Cmax of 40% to 50% is not considered clinically important since the impact is confined to a systemic compartment in which the drug does not have pharmacological

effect and is present at very low concentration. Also, the rise in lomitapide plasma concentration observed immediately after dialysis is suggestive of haemoconcentration, which may partially explain the increase in lomitapide plasma concentrations. Finally, any impact of renal function on systemic pharmacokinetics would be mitigated by the adjustment in dosing over time, designed to accommodate individual patient responsiveness in terms of efficacy and safety.

Documented diagnosis of any of the following pulmonary conditions: Asthma, Chronic obstructive pulmonary disease, Idiopathic pulmonary fibrosis

Reason for exclusion:

These patients were excluded from clinical trials based upon the non-clinical finding of pulmonary histiocytosis in rats, the significance of which was unknown.

Is it considered to be included as missing information?

No.

Rationale

Based upon the findings in rats, pulmonary function tests were included in clinical trials. Lomitapide in doses up to 60 mg for a total treatment period of 78 weeks did not produce clinically significant changes in any pulmonary function parameters. Thus, no safety concerns were raised and there is no reason to contraindicate lomitapide in these patients who may derive benefit from the drug.

Current use of corticosteroids or betaine.

Reason for exclusion:

Corticosteroids may cause or exacerbate fatty liver disease. The combination with lomitapide was avoided in the clinical trials in order to avoid confounding the effect of lomitapide on steatosis. Betaine is a dietary supplement sometimes used to ameliorate fatty liver disease. The use of betaine would likely identify patients with pre-existing fatty liver disease. Patients with known baseline steatosis were excluded to avoid exacerbating and confounding the effect of lomitapide on accumulation of hepatic fat

Is it considered to be included as missing information?

No.

Rationale

Although corticosteroids may cause hepatic steatosis there is no evidence that this directly increases the risk of progressive liver disease. It is possible that weight gain and insulin resistance caused by corticosteroid use may be the causative factor. The direct anti-inflammatory effect of corticosteroids has been proposed as a benefit in patients at risk of NASH. There are no data to suggest that combination with lomitapide increases the risk of progressive liver disease.

Betaine is not known to cause liver injury. It has been proposed to reduce hepatic fat accumulation. Therefore, there is no reason to contraindicate combined use with lomitapide.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

TYPE OF SPECIAL POPULATION	EXPOSURE
Paediatric population	Patients under the age of 5 were excluded in clinical trials. As the safety and efficacy of Lojuxta in children < 5 years have not been established, the use of this medicinal product in children less than 5 years is not recommended.
Elderly population	No elderly subjects aged >75 were included in any clinical study. A limited number of patients (N=97) of ≥ 65-74 were included in the phase 2 trials, however, no elderly HoFH patients were included.
Pregnant women	Pregnant patients were excluded in clinical trials and pregnancy is a contraindication to lomitapide use.
Breastfeeding women	It is not known if lomitapide is excreted into breast milk. The SmPC provides specific advice regarding whether to discontinue breast-feeding or discontinue the medicinal product.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	These patients were excluded from the clinical trial programme. No full renal impairment study was conducted; subjects with mild and moderate renal impairment were excluded from clinical trials. The SmPC provides specific advice regarding monitoring of liver function.
Population with relevant different ethnic origin Use in Non-Caucasian population	86% of the patients in clinical trials with HoFH were of Caucasian origin.
Subpopulations carrying relevant genetic polymorphisms	HoFH is a genetic disease that is inherited in an autosomal dominant fashion from both parents. Patients must have 2 mutations in the LDL receptor gene or genes known to affect LDL receptor function. Since lomitapide directly inhibits the generation of LDL-C and is not dependent on LDL receptor function, the type of genetic mutation would not be expected to impact the efficacy or safety of lomitapide.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Non-study Post-authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Patient exposure from marketing experience was calculated based on estimation of cumulative patient exposure since the launch date in the US i.e, 28 January 2013. In the PSUR 14 interval patient exposure was calculated based on absolute patient exposure numbers which are monitored by the commercial team. The cumulative patient exposure was calculated adding the interval new starts to the previous cumulative data from PSUR 13. Patients who restarted therapy during the period were not included in the cumulative figure again.

A patient exposure estimation has also been provided based on interval sales data and the cumulative patient exposure was calculated adding the interval to the previous cumulative number. The following formula was used to calculate interval and cumulative patient exposures:

Number of mg sold (mg) ÷ average daily dose (40 mg per day) ÷ 1 year (365) = number of patient years

Of note, there have been limitations in receiving information on patient gender, age and ethnicity from suppliers (in some territories) or when receiving requests from pharmacies in all territories. Patient privacy laws are adhered to in each territory, and as a result, this information is not readily available for all countries. Therefore, detailed information on gender and age is provided only for regions in which these data are available, namely US.

SV.1.2 Exposure

Cumulatively, up to 31 July 2024, 2,259 estimated patients have been exposed worldwide to lomitapide, including 1637 in the US, 281 in EEA and 341 in the rest of the world.

Table 10. Cumulative Exposure from the Marketing Experience to Lomitapide

		TOTAL NUMBER OF PATIENTS UP TO 31 JUL 2024
Sex[1]	**Male**	622
	Female	1015
Age (Years)[1]	**<2**	0
	2 to 17	26
	>18 to 65	1132
	>65	479
Regions	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	EEA and UK	281

		TOTAL NUMBER OF PATIENTS UP TO 31 JUL 2024
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Total by Region		**2,259**

1 US data only- number of unique naïve patients having received JUXTAPID for the first time within the reporting period

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Lomitapide is not associated with abuse or dependence. Therefore, no potential for misuse for illegal purposes is anticipated.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

Safety Concerns
Identified Risks - Effects on the liver. - Nausea, diarrhoea, weight loss and poor absorption of fat-soluble vitamins and essential fatty acids. - Interaction with statins (a type of drug which lowers cholesterol by a different mechanism to Lojuxta) **Potential Risks** - Hepatic fibrosis (scarring of the liver) - Liver tumours - Intestinal tumours - Pancreatic tumours - Use for conditions other than that for which Lojuxta is approved (Off label use) - Unintended pregnancy **Missing information** - Use during pregnancy - Use in children - Use with alcohol - Use in non-Caucasian patients - Use in patients who already have liver disease - Use in patients who are taking other drugs which may affect the liver

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Some adverse reactions listed in the Summary of Product Characteristics (SmPC) are not considered important for inclusion in the list of safety concerns in the RMP. These undesirable effects are listed and discussed below.

- SOC Infections and infestations: gastroenteritis, gastrointestinal infection, influenza, nasopharyngitis, sinusitis are adverse reactions listed in section 4.8 of the SmPC but are not associated to a relevant risk.
- SOC Blood and lymphatic system disorders: anemia is an adverse reaction listed in section 4.8 of the SmPC, but it is not associated to a relevant risk.
- SOC Metabolism and nutrition disorders: decreased appetite and dehydration are adverse reactions listed in section 4.8 of the SmPC but are not associated to a relevant risk.
- SOC Nervous system disorders: paraesthesia, somnolence, dizziness, headache, migraine are adverse reactions listed in section 4.8 of the SmPC but are not associated to a relevant risk.
- SOC Eye disorders: eye swelling is an adverse reaction listed in section 4.8 of the SmPC but is not associated to a relevant risk.
- SOC Ear and labyrinth disorders: vertigo is an adverse reaction listed in section 4.8 of the SmPC but is not associated to a relevant risk.
- SOC Respiratory, thoracic and mediastinal disorders: pharyngeal lesion, upper-airway cough syndrome are adverse reactions listed in section 4.8 of the SmPC but are not associated to a relevant risk.
- SOC Gastrointestinal disorders: flatulence, vomiting, abdominal discomfort, dyspepsia, abdominal pain, abdominal pain upper, abdominal pain lower, flatulence, abdominal distension, constipation, gastritis, rectal tenesmus, aerophagia, defaecation urgency, eructation, frequent

bowel movements, gastric dilatation, gastric disorder, gastroesophageal reflux disease, haemorrhoidal haemorrhage, regurgitation, dry mouth, faeces hard, abdominal tenderness, epigastric discomfort, , haematemesis, lower gastrointestinal hemorrhage, reflux oesophagitis are adverse reactions listed in section 4.8 of the SmPC, but are not associated to a relevant risk.

- SOC Hepatobiliary disorders: hepatomegaly is an adverse reaction listed in section 4.8 of the SmPC but is not associated to a relevant risk.
- SOC Skin and subcutaneous tissue disorders: blister, dry skin, hyperhidrosis, ecchymosis, papule, rash erythematous, xanthoma, alopecia are adverse reactions listed in section 4.8 of the SmPC but are not associated to a relevant risk.
- SOC Musculoskeletal and connective tissue disorders: muscle spasms, arthralgia, myalgia, pain in extremity, joint swelling, muscle twitching are adverse reactions listed in section 4.8 of the SmPC but are not associated to a relevant risk.
- SOC Renal and urinary disorders: haematuria is an adverse reaction listed in section 4.8 of the SmPC but is not associated to a relevant risk.
- SOC General disorders and administration site conditions: fatigue, asthenia, chest pain, chills, early satiety, gait disturbance, malaise, pyrexia are adverse reactions listed in section 4.8 of the SmPC but is not associated to a relevant risk.
- SOC Investigations: neutrophil count decreased, white blood cell count decreased, neutrophil percentage increased, protein urine, pulmonary function test abnormal, white blood cell count increased, blood potassium decreased, carotene decreased, prothrombin time prolonged, vitamin E decreased, vitamin K decreased are adverse reactions listed in section 4.8 of the SmPC, but are not associated to a relevant risk.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

All of the above listed risks are those with minimal clinical impact on patients (in relation to the severity of the indication(s) treated).

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risk 1: Hepatic effects (elevated aminotransferases, hepatic steatosis)

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 and the paediatric APH-19 study.

Across the lomitapide programme, 5 adult studies included an evaluation of hepatic fat. Review of scatter plots across these 5 adult studies showed no apparent relationship between exposure to lomitapide (based on average or nominal dose or total lomitapide dose) and maximum hepatic fat percent.

The most frequently reported side effects in the paediatric APH-19 study, were hepatic abnormalities, that resolved with dose reduction or suspension. Hepatic TEAEs were reported for 23 (53.5%) subjects overall, with similar frequency in the 2 age groups (5 to 10 years and 11 to 17 years). The most frequently reported hepatic TEAEs were ALT increased and AST increased, reported for 39.5% and 34.9% of subjects, respectively. Hepatic fat accumulation was mild and consistent with published evidence for adults.

In the post-marketing setting, cumulatively through 31 July 2024, there were 612 ICSRs (450 solicited, 134 spontaneous, 28 literature) reporting 902 hepatic events.

Risk-benefit impact: Patients with mild elevations of liver function tests are likely to be asymptomatic. Mild elevations in liver chemistry tests such as ALT and AST can reveal serious underlying conditions or have transient and benign aetiologies (Giboney, 2005 Am Fam Physician). Indeed, in many instances, liver disease is diagnosed in asymptomatic subjects who have been found to have abnormal hepatic enzyme levels as part of routine screening (Ghany, 2011 Harrison's Principles of Internal Medicine). Abnormal ALT/AST may accompany hepatic steatosis, which also is often asymptomatic. However, if liver damage progresses, patients develop symptoms such as nausea, weight loss, jaundice, abdominal pain and malaise. Progressive liver disease may have a fatal outcome.

Subjects with pure steatosis have a benign prognosis: follow-up of 198 subjects for up to 21 years revealed progression to cirrhosis in 3 subjects and liver-related death in only 1 subject (Adams, 2005 CMAJ). However, the prognosis is worse if, in addition to hepatic fat accumulation, evidence of hepatocellular inflammation and damage emerges (steatohepatitis): up to 11% of these subjects may die of liver-related causes.

Important identified risk 2: Gastrointestinal effects (nausea, diarrhoea, weight loss, malabsorption of fat-soluble vitamins, decline in essential fatty acids)

In the adult clinical development programme, 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 paediatric study APH-19, treatment emergent adverse events in the MedDRA SOC of Gastrointestinal disorders were reported for 31 (72.1%) subjects. All were mild or moderate in severity. No gastrointestinal TEAEs were reported as SAEs. Similar proportions of subjects in each age group experienced gastrointestinal TEAEs; 13 (65.0%) subjects 5 to 10 years and 18 (78.3%) subjects 11 to 17 years. The most frequently reported TEAEs by PT were diarrhoea, abdominal pain, and vomiting. Diarrhoea and abdominal pain were reported by similar proportions of subjects 5 to 10 years (45.0% and 40.0%, respectively) and subjects 11 to 17 years (56.5% and 47.8%, respectively). Vomiting had a higher incidence in subjects 5 to 10 years (50.0%) compared to subjects 11 to 17 years (8.7%).

In the post-marketing setting, cumulatively, through 31 Jul 2024, there were 1909 ICSRs (1379 solicited, 509 spontaneous, 21 literature) reporting 3492 GI events.

Risk-benefit impact: Vomiting is the main complication of nausea and may lead to symptomatic dehydration and electrolyte abnormalities in severe cases (Greenberger, 2008 The Merck Manual for Health Care Professionals). Chronic vomiting can result in undernutrition, weight loss and metabolic abnormalities. Similarly, diarrhoea may also induce dehydration and electrolyte abnormalities (Bharucha, 2007 The Merck Manual for Health Care Professionals).

Diarrhoea may vary in severity. Severe diarrhoea may also lead in some cases to dehydration.

The malabsorption of fat-soluble vitamins may result in various complications, including night blindness (vitamin A), bruising or bleeding (vitamin K) and pathologic fractures (vitamin D) (Ruiz, 2008 The Merck Manual for Health Care Professionals).

Essential fatty acid deficiency can cause an array of symptoms in virtually all organs of the human body, including skin rashes, decreased haematopoiesis, pulmonary complications, increased susceptibility to infections and hepatic steatosis (Yamanaka, 1980 Prog Lipid Res).

Important identified risk 3: Rhabdomyolysis with or without acute renal failure due to interaction with statins

In the adult 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.

Overall, 5 subjects (11.6%) were reported with TEAEs in the SOC musculoskeletal and connective tissue disorders, all aged 11 to 17 years in the APH-19 paediatric study. Arthralgia was reported for 2 subjects, and exostosis, myalgia, and tendon disorder were reported for 1 subject each. The TEAE of myalgia (Subject 03/01, Day 251) was mild, unrelated to study drug, and resolved without treatment or dose change after 6 days. The subject was taking ezetimibe (10 mg QD) and atorvastatin (80 mg QD). This subject did not experience an increase of CK during the study.

In the post-marketing setting, cumulatively up to 31 July 2024, there were 2 spontaneous cases of potential interaction between lomitapide and statins. The first case reported a non-serious event of Liver function test increased. The second case reported a non-serious event of Low-density lipoprotein increased. No cases cumulatively reported rhabdomyolysis due to an interaction with statins.

Risk-benefit impact: If left unrecognised and untreated, it may lead to renal failure and potential fatality. The impact on individual patient liver disease is discussed under “Identified Risk: Hepatic events” in this Module VII. Rhabdomyolysis presents initially with muscle pain, tenderness or weakness which is a well-documented side effect of statin therapy, and this risk is greater with concurrent use of drugs that inhibit cytochrome p450-3A4 (CYP3A4).

Important potential risk 1: Hepatic fibrosis

Clinical Study: No cases of hepatic fibrosis were observed in CTs with lomitapide.

Post-marketing experience: Cumulatively, up to 31 Jul 2024, were 4 cases of serious Hepatic fibrosis.

Risk-benefit impact: Hepatic fibrosis is asymptomatic but can lead to serious complications such as portal hypertension and cirrhosis (Shaffer, 2007 The Merck Manual for Healthcare Professionals).

Important potential risk 2: Primary hepatic tumours

Clinical Study: No cases of benign or malignant liver neoplasms were observed in CTs with lomitapide.

Post-marketing experience: Cumulatively, 2 cases reporting Primary hepatic tumour have been reported from the postmarketing sources up to 31 Jul 2024. One serious solicited ICSR 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. Another serious solicited ICSR concerned an 81-year-old female patient who on an unspecified date, the patient was in the hospital with newly diagnosed liver and uterine cancer. Her physician recommended to stop taking lomitapide. The patient passed away. The reporter did not provide a causal relationship between the reported events and lomitapide. Due to limited information on the concomitant medications, complete medical history (including previous malignancies), duration of lomitapide treatment, details on circumstances surrounding the death of the patient, cause of death,

concurrent conditions, relevant laboratory investigation reports, autopsy details, etc., it is not possible to make a conclusive assessment.

Risk-benefit impact: Hepatocellular carcinoma may be symptomless in the early stages and patients may present with symptoms when the condition is further advanced and treatment options limited leading to fatality.

Important potential risk 3: Small bowel / intestinal tumours

Clinical Study: No cases of benign or malignant intestinal neoplasms were observed in Clinical Studies.

Post-marketing experience: One case reporting a small intestine carcinoma was identified up to 31 July 2024. 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-benefit impact: Patients may initially present with non-specific gastro-intestinal symptoms. Early investigation of such symptoms is required in order to identify the condition at an early stage to allow for potential treatment options.

Important potential risk 4: Pancreatic tumours

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 July 2024. 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. Note, this is the same case described in Hepatic Tumours.

Risk-benefit impact: Patients may initially present with non-specific gastro-intestinal symptoms. Early investigation of such symptoms is required in order to identify the condition at an early stage to allow for potential treatment options.

Important potential risk 5: Unintended pregnancy

There were no reports of unintended pregnancy in the clinical development programme. In the post-marketing setting, there were 5 reports of non-serious cases of unintended pregnancy reported. One ICSR was terminated via abortion due to social reasons, and the other 4 ICSRs resulted in healthy infants.

Risk-benefit impact: Unintended pregnancy may have significant medical and social implications for the patient.

Missing Information 1: Use during Pregnancy

The safety profile in pregnancy could not be determined from this small data.

Missing Information 2: Use in children

The safety profile of lomitapide in children < 5 years has not yet been established from the current clinical development programme.

Missing Information 3: Use with Alcohol

The effect of lomitapide on use with alcohol could not be determined from the current clinical development programme.

Missing Information 4: Use in non-Caucasian patients

The safety profile of use in non-Caucasian patients could not be determined from this small data.

Missing Information 5: Use in patients who already have liver disease

The effect of lomitapide on patients with liver disease could not be determined from the current clinical development programme.

Missing Information 6: Use in patients who are taking other drugs which may affect the liver

The effect of lomitapide on patient who are taking other hepatotoxic agents could not be determined from the current clinical development programme.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Missing information: Use in children updated to Missing information: Long term safety in children.

SVII.3 Details of important risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risk: Hepatic Effects

Potential mechanisms:

Hepatic steatosis may be the consequence of MTP inhibition, which blocks triglyceride transfer to VLDL (the precursor of LDL) (Joy, 2008 Nat Clin Pract Cardiovasc Med). AST and ALT elevations are probably related to the mechanism of action of lomitapide in the liver. However, this condition seems to be reversible with treatment discontinuation.

Evidence source(s) and strength of evidence:

Clinical trials:

Adult studies: In Study UP100, 4 patients presented with elevated liver investigations (66.7%). In Study UP1002 (AEGR-733-005), 2 patients experienced Hepato-biliary disorders (6.9%), 8 patients presented with elevated liver investigations (27.6%).

Paediatric study: In APH-19 study the most frequently reported hepatic TEAEs were ALT increased, and AST increased, reported for 39.5% and 34.9% of subjects, respectively.

Post-Marketing: Cumulatively through 31 July 2024, there were 612 ICSRs (450 solicited, 134 spontaneous, 28 literature) reporting 902 hepatic events.

Characterisation of the risk:

Elevated aminotransferases

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.

In the Phase 3 major effectiveness study (UP1002/AEGR-733-005) in subjects with HoFH, where the dose of lomitapide was escalated to the maximum tolerated dose, 3 subjects experienced elevations in ALT and/or AST between 5 and 10×ULN. In one additional subject, ALT reached 10.6×ULN. There were no significant changes in total bilirubin or alkaline phosphatase associated with these elevations. The initial transaminase elevations to >5×ULN all occurred during the dose escalation phase of the study (at Week 6 in 3 of the 4 subjects and at Week 14 in one). The transaminase elevations in these 4 subjects resolved rapidly (7 to 28 days) with dose interruptions or reductions and all 4 subjects successfully completed the study through Week 78. Review of subjects with elevations in ALT >3 and ≤ 5×ULN indicated that some subjects have transaminase levels return to <3×ULN without dose reduction or interruption. Median time to occurrence of ALT or AST to >3×ULN was 126.5 days.

In the extension study, one subject discontinued lomitapide treatment due to not being able to maintain aminotransferases <5×ULN which may have been related to alcohol intake. One subject in this study had an ALT elevation of 24×ULN with AST of 13×ULN; bilirubin levels were within normal range. The elevations were reported as a serious adverse event and occurred in the setting of concomitant medications known to cause liver injury (agomelatine and clarithromycin) which were considered likely to have played a role in the event. Lomitapide and both of these agents were discontinued and aminotransferase levels returned rapidly towards normal (within 2 weeks). Histology from a liver biopsy obtained approximately 2 months later demonstrated the presence of mild steatosis without significant inflammation or fibrosis. Lomitapide treatment was re-started in this subject without clinical consequence and ALT and AST levels remained <2×ULN.

In the paediatric APH-19 study, one subject (in the 5 to 10 years age group) experienced a severe SAE of transaminases increased that was considered related to study treatment, met the criteria for a Level 4 Hepatotoxicity per APH-19 study protocol and was therefore reported as an Adverse Event of Special Interest (AESI) to the Data Safety Monitoring Board (DSMB). Lomitapide was interrupted and later successfully re-challenged. In addition, 2 subjects experienced mild AESIs of hepatic steatosis that resolved without any action taken. For 1 of these subjects, an additional mild AESI of hepatomegaly was reported. Of note, in both subjects, hepatic fat was assessed using ultrasound as being ≤10% throughout the study.

Few subjects exceeded hepatotoxicity thresholds (>3 × ULN or higher) for AST or ALT, and none for total bilirubin. The highest ALT abnormalities reported were >5 to ≤10 × ULN for 2 subjects, and >3 to ≤5 × ULN for 3 subjects. For AST, 3 subjects reported values >3 to ≤5 × ULN. There were no values >5 × ULN reported for AST. No subject discontinued treatment permanently due to LFT elevations and all elevations were managed either by dose reduction or temporary interruption of lomitapide as per protocol.

Hepatic fat accumulation

Accumulation of hepatic fat is an expected consequence of MTP inhibition and reflects the pharmacological effect of lomitapide. In lomitapide-treated subjects, accumulation of hepatic fat plateaus in most subjects, decreases in some during continued treatment, and is rapidly reversible following treatment cessation.

In study UP1002/AEGR-733-005, hepatic fat content data are available at baseline and Week 26, 56 and 78. Mean percent hepatic fat was <1% at baseline and was 9% and 8% at Weeks 26 and 78, respectively.

The majority of subjects with hepatic fat assessments during the study (13 of 23, 57%) had maximum percent hepatic fat levels <10% during the 78-week treatment period. Percent hepatic fat was >20% in 3 subjects. In 2 of these 3 subjects the hepatic fat was >20% at the first assessment (Week 26) and in the third subject the increase to >20% was at Week 56. The 3 subjects were receiving lomitapide doses of 60 mg, 60 mg and 5 mg, respectively, at the time of the hepatic fat elevation of >20%. Two subjects had hepatic fat levels decline during continued treatment with lomitapide; in 1 subject this occurred during continued dosing with 60 mg and in the other, dose reduction and interruption related to transaminase elevations were implemented prior to the next assessment. One subject had hepatic fat levels continue to increase at a dose of 5 mg with a maximum of 44% reported at Week 61; this subject completed the study through Week 78. At the post-treatment assessment (Week 84; 6 weeks off treatment), computed tomography scan was conducted (subject refused nuclear magnetic resonance imaging due to metal implants) which indicated hepatic fat content had decreased to between 7 to 15%. Follow-up data were available for 3 additional subjects with hepatic fat >10% on study; all 3 had rapid reduction in the levels of hepatic fat off treatment.

The rapid reversal in hepatic fat following discontinuation of treatment also was observed in the Phase 2 HoFH study and in another Phase 2 study (CV145-009) conducted in subjects with elevated LDL-C, which was specifically designed to assess reversibility in hepatic fat.

In the Phase 2 HoFH study, mean change from baseline in percent hepatic fat to Week 16 (end of treatment) was 19%; after 4 weeks off treatment, the mean change from baseline was 5%, demonstrating the rapid reversibility in the accumulation of hepatic fat. Similarly, in Study CV145-009, which evaluated a 25 mg dose of lomitapide administered for 4 weeks, the mean increase from baseline in hepatic fat content to Week 4 was 21%. Six weeks after discontinuation of dosing, the change from baseline in mean percent hepatic fat content was 4%, again demonstrating the rapid reversibility in the accumulation of hepatic fat.

In APH-19 paediatric study, the majority of subjects in both age groups (5 to 10 years and 11 to 17 years) remained at or below 10% liver fat at all time points. Only 1 subject in the 11 to 17 years age group had an increase in liver fat to >20% at Week 24, while 2 subjects in the 11 to 17 years age group and 1 subject in the 5 to 10 years age group had liver fat results of 18% or 19% during the study. Subjects with valid NMR scans had a median hepatic fat content of 3.28% at Baseline that increased to 7.48% at Week 24, 7.96% at Week 56, and 6.70% at Week 104. Thus, median hepatic fat increases were stable after Week 24. At the Week 108 Follow-up visit, median hepatic fat decreased to 3.23%, near Baseline levels. These data indicate that hepatic fat accumulation was reversible after discontinuation of lomitapide. It should be noted, however, that Week 108 data were available from only 7 subjects, because the Week 108 visit was conducted in person only for subjects who had discontinued lomitapide treatment at Week 104 (because they did not wish to or could not at the time continue treatment through the EAP or with the commercial product).

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.

Although lomitapide may cause hepatic steatosis in some subjects, it is not clear what proportion, if any, will go on to develop nonalcoholic steatohepatitis or other related conditions. The long-term effect of hepatic fat accumulation due to MTP inhibition is unknown.

Clinical experience

SAFETY CONCERNS FROM HIGHER LIVER FUNCTION TEST RESULTS POST FIRST DOSE: STUDY UP1002/AEGR-733-055 (N=29)			
PREFERRED TERM (PT)	**N**	**FREQUENCY PER 100**	**95% CI**
ALT			
> 3 to ≤ 5 x ULN	6	20.7	8.0-39.7
> 5 ≤ 10 x ULN	3	10.3	2.2-27.4
>10≤ 20 x ULN	1	3.4	0.1-17.8
>20 x ULN	0	0.0	0.0-11.9
AST			
> 3 to ≤ 5 x ULN	5	17.2	5.8-35.8
> 5 ≤ 10 x ULN	1	3.4	0.1-17.8
>10≤ 20 x ULN	0	0.0	0.0-11.9
>20 x ULN	0	0.0	0.0-11.9

SAFETY CONCERNS FROM SERIOUSNESS AND SEVERITY OF HEPATIC AES STUDY UP1001 (N=6)			
PREFERRED TERM (PT)	**N**	**FREQUENCY PER 100**	**95% CI**
TEAE	4	66.7	22.3-95.7
Treatment Related TEAE	4	66.7	22.3-95.7
Serious TEAE	0	0.0	0.0-45.9
Serious Treatment Related TEAE	0	0.0	0.0-45.9
Severe TEAE	3	50.0	11.8-88.2
Severe Treatment Related TEAE	3	50.0	11.8-88.2
TEAE Resulting in Treatment Discontinuation	0	0.0	0.0-45.9
TEAE resulting in Death on Study	0	0.0	0.0-45.9

SAFETY CONCERNS FROM SERIOUSNESS AND SEVERITY OF HEPATIC AES – STUDY UP1002/AEGR-733-005 (N=29)			
PREFERRED TERM (PT)	**N**	**FREQUENCY PER 100**	**95% CI**
TEAE	8	27.6	12.7-47.2
Treatment Related TEAE	7	24.1	10.3-43.5
Serious TEAE	0	0.0	0.0-11.9
Serious Treatment Related TEAE	0[a]	0.0	0.0-11.9
Severe TEAE	3	10.3	2.2-27.4
Severe Treatment Related TEAE	3	10.3	2.2-27.4
TEAE Resulting in Treatment Discontinuation	0[b]	0.0	0.0-11.9
TEAE resulting in Death on Study	0	0.0	0.0-11.9

a One subject was discontinued from lomitapide during the extension study due to not being able to maintain aminotransferases < 5×ULN which may have been related to alcohol intake.
b One subject had an SAE of 'hepatotoxicity' during the extension study with ALT 24×ULN in the setting of concomitant medications known to cause liver injury (agomelatine and clarithromycin) which were considered likely to have played a role in the event.

HEPATIC TREATMENT EMERGENT RELATED ADVERSE EVENTS – STUDY APH- 19	
	PAEDIATRIC HOFH (5 TO 17 YEARS)
PREFERRED TERM	STUDY APH-19 (N=43) N (%)
Alanine aminotransferase increased	13 (30.2)
Aspartate aminotransferase increased	13 (30.2)
Transaminases increased	5 (11.6)
Hepatic steatosis	2 (4.7)
Alanine aminotransferase abnormal	1 (2.3)
Hepatomegaly	1 (2.3)
Ultrasound liver abnormal	1 (2.3)
Hepatotoxicity	0
International normalised ratio increased[1]	0
International normalised ratio abnormal[1]	0
Blood Alkaline Phosphatase Increased	0

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 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 study of 1,313 Taiwanese subjects (Yueh, 2011 Diabetes Res Clin Pract).

Insulin resistance, obesity, diabetes and dyslipidemia 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.

Preventability:

Information is provided in the SmPC in Section 4.3 and Section 4.4. The SmPC contraindicates use of Lojuxta in patients with moderate to severe hepatic impairment and those with persistent unexplained 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. It recommends measuring hepatic enzymes (ALT, AST, alkaline phosphatase, gamma-glutamyl transferase [gamma-GT]), total bilirubin and serum albumin before initiation of treatment with Lojuxta and prior to each dose escalation or monthly, whichever occurs first. After the first year of treatment, hepatic enzymes should be monitored at least every 3 months and before any increase in dose. A gradual dose escalation is recommended in order to minimise the incidence and severity of aminotransferase elevations, and detailed recommendations in case of AST/ALT elevations are also provided.

See Section Important Potential Risk: Hepatic Fibrosis for screening recommendations for steatohepatitis and fibrosis.

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.

Clinical data from phase 2/3 demonstrate that hepatic enzyme elevations were reversible on dose reduction or interruption in lomitapide treatment.

Additionally, educational materials for prescribers and patients will be provided. Refer to V.3 Summary of risk minimisation measures Table V 2

Impact on the risk-benefit balance of the product:

Patients with mild elevations of liver function tests are likely to be asymptomatic. Mild elevations in liver chemistry tests such as ALT and AST can reveal serious underlying conditions or have transient and benign aetiologies (Giboney, 2005 Am Fam Physician). Indeed, in many instances, liver disease is diagnosed in asymptomatic subjects who have been found to have abnormal hepatic enzyme levels as

part of routine screening (Ghany, 2011 Harrison's Principles of Internal Medicine). Abnormal ALT/AST may accompany hepatic steatosis, which also is often asymptomatic. However, if liver damage progresses, patients develop symptoms such as nausea, weight loss, jaundice, abdominal pain and malaise. Progressive liver disease may have a fatal outcome

Subjects with pure steatosis have a benign prognosis: follow-up of 198 subjects for up to 21 years revealed progression to cirrhosis in 3 subjects and liver-related death in only 1 subject (Adams, 2005 CMAJ). However, the prognosis is worse if, in addition to hepatic fat accumulation, evidence of hepatocellular inflammation and damage emerges (steatohepatitis): up to 11% of these subjects may die of liver-related causes.

Public health impact:

Although NAFLD can lead to hepatocellular carcinoma and is associated with several cardiovascular risk factors, its impact on mortality is unknown. Results from studies on the association between NAFLD and mortality have been inconsistent, but these studies were limited by the use of small, highly selected subject populations (for example, those after liver biopsy) or by the use of liver enzyme measurements as surrogate markers of NAFLD. Furthermore, since NAFLD is strongly associated with obesity and diabetes, whether it is an independent risk factor for all cause and cardiovascular death remains controversial, as many previous studies failed to account fully for adiposity (Lazo, 2011 BMJ).

AST and ALT elevations associated with lomitapide are generally dose-dependent and typically resolve upon dose reduction or interruption. The long-term consequences of hepatic fat accumulation due to MTP inhibition are unknown.

Important Identified Risk: Gastrointestinal effects (nausea, diarrhoea, weight loss, malabsorption of fat-soluble vitamins, decline in essential fatty acids)

Potential mechanisms:

As part of its mechanism of action, lomitapide causes intestinal triglyceride accumulation via MTP inhibition. Presumably, the GI symptoms discussed in this section are related to this action (Samaha, 2008 Nat Clin Pract Cardiovasc Med).

Evidence source(s) and strength of evidence:

Clinical Trials: *In Study UP1001, 5 patients experienced gastrointestinal disorders (83.3%). In study UP1002 (AEGR-733-005), 27 patients experienced gastrointestinal disorders (93.1%). In APH-19 study, Treatment emergent adverse events in the SOC of Gastrointestinal disorders were reported by 72.1% of subjects with slightly lower incidence in subjects 5 to 10 years (65.0% of subjects) than 11 to 17 years (78.3% of subjects).*

Post-marketing: *Cumulatively, through 31 July 2024, there were 1909 ICSRs (1379 solicited, 509 spontaneous, 21 literature) reporting 3492 GI events.*

Post-marketing experience

With the exception of diarrhoea, post marketing data has not revealed any change to the characterisation of this risk.

Data from post-marketing experience up to 31 July 2024 has revealed 1199 reports of diarrhoea, 149 (12.4%) were serious. Of the 149 serious events, 105 recovered, 5 were recovering, 13 did not recover and outcome was unknown in the remaining 26 events.

Characterisation of the risk:

Gastrointestinal disorders were the most common type of treatment-related TEAEs, with 32 (91%) of 35 HoFH subjects experiencing at least one GI disorder, including 83% and 93% of subjects in Study UP1001 and Study UP1002/AEGR-733-005, respectively. Within this SOC, the most common GI disorders were diarrhoea (28 subjects; 80%), nausea (21 subjects; 60%), vomiting (12 subjects; 34%), dyspepsia (11 subjects; 31%), and abdominal discomfort (9 subjects; 26%). None of the GI disorders were reported as serious adverse events.

Although GI adverse effects were frequently observed during treatment with lomitapide, the majority of the events were mild to moderate in severity. Review of the incidence of GI events by 4-week intervals during Study UP1002/AEGR-733-005 showed that the incidence was highest during dose escalation; once subjects reached their maximum tolerated dose, the incidence of GI events decreased. Overall, 12 subjects had at least one dose reduction or interruption of 3 or more days during the study that were related to gastrointestinal adverse events. Four of these subjects had both a reduction and an interruption, 6 had only a reduction, and 2 had only an interruption. Among the 12 subjects with a dose modification related to gastrointestinal adverse events, 8 were re-challenged at or above the dose prior to the dose modification, including 6 of 10 subjects who had a dose reduction and 5 of 6 who had a dose interruption.

Among the 6 subjects with interruptions of 3 or more days reported on the dosing record for gastrointestinal adverse events, the first interruption ranged from 3 to 8 days; median duration of the interruption was 5 days. Three of these 6 subjects had subsequent interruptions for durations of 4 to 5 days for gastrointestinal adverse events.

Three subjects discontinued treatment due to GI adverse events in Study UP1002/AEGR-733-005. Review of dietary compliance indicated that these subjects did not follow the low-fat diet (<20% energy from fat) emphasizing the importance of dietary compliance during treatment with lomitapide. There was no difference in the incidence of GI AEs for subjects who received apheresis (17 of 18 subjects, 94%) during lomitapide treatment and those who did not (10 of 11 subjects, 91%).

Adverse event incidence based on type of concomitant statin was evaluated in Study UP1002/AEGR-733-005. The incidence of diarrhoea was higher in subjects who received concomitant atorvastatin or simvastatin (93%) compared with subjects who received concomitant rosuvastatin (69%), as were the incidences of vomiting (50% versus 15%), abdominal pain (36% versus 15%), and weight decreased (36% versus 15%).

There were no significant correlations between change in weight and number of diarrhoea events at Weeks 26 or 78; however, there was a significant, although modest, correlation between change in weight and diarrhoea events at Week 36. The most commonly administered types of treatment for GI AEs, primarily reported for diarrhoea, were antipropulsives, including loperamide and Lomotil (diphenoxylate and atropine); mebeverine was also used for both diarrhoea and abdominal bloating/cramping.

Nausea and diarrhoea are very common conditions for which subjects do not necessarily seek medical attention. An Australian review of 596,000 subject visits to general practitioners showed nausea and/or vomiting as the primary reason for encounters in 1.6% of cases (Britt, 2007 Aust Fam Physician).

A UK study of over 8,000 adults surveyed over a 4-month period revealed that 633 of them (7.9%) had at least one episode of diarrhoea during the previous month (Feldman, 1994 Epidemiol Infect). Other studies of Western populations found comparable incidences of chronic diarrhoea (4-5%), although the disorder becomes more common with age (Thomas, 2003 Gut). Of note, British guidelines define chronic diarrhoea as the abnormal passage of three or more loose or liquid stools per day for more than four weeks and/or a daily stool weight greater than 200 g/day (Thomas, 2003 Gut).

In APH-19, the most common gastrointestinal TEAEs were diarrhoea (51.2% of subjects) and abdominal pain (44.2% of subjects). Vomiting was reported by 27.9% subjects overall with a higher incidence in subjects 5 to 10 years (50.0%) compared to subjects 11 to 17 years (8.7%). Most were mild or moderate in severity. Dose reduction or interruption for gastrointestinal events was reported in 11 subjects (25.6%). The pattern of gastrointestinal AEs varied slightly from the one seen in adults, who reported abdominal pain less frequently (27.6% of adult subjects) and diarrhoea more frequently (79.3% of adult subjects).

Two subjects in the 11 to 17 years age group prematurely discontinued the study due to AESIs of diarrhoea after the doses of lomitapide had been escalated at Week 8 to 10 mg and 20 mg, respectively.

Clinical experience

SAFETY CONCERNS FROM SERIOUSNESS AND SEVERITY OF GI AES STUDY UP1001 (N=6)			
PREFERRED TERM (PT)	**N**	**FREQUENCY PER 100**	**95% CI**
TEAE	5	83.3	35.9-99.6
Treatment Related TEAE	5	83.3	35.9-99.6
Serious TEAE	0	0.0	0.0-45.9
Serious Treatment Related TEAE	0	0.0	0.0-45.9
Severe TEAE	0	0.0	0.0-45.9
Severe Treatment Related TEAE	0	0.0	0.0-45.9
TEAE Resulting in Treatment Discontinuation	0	0.0	0.0-45.9
Resulting in Death on Study	0	0.0	0.0-45.9
SERIOUSNESS AND SEVERITY OF GI AES STUDY UP1002/AEGR-733-005 (N=29)			
PREFERRED TERM (PT)	**N**	**FREQUENCY PER 100**	**95% CI**
TEAE	27	93.1	77.2-99.2
Treatment Related TEAE	25	86.2	68.3-96.1
Serious TEAE	0	0.0	0.0-11.9
Serious Treatment Related TEAE	0	0.0	0.0-11.9
Severe TEAE	6	20.7	8.0-39.7
Severe Treatment Related TEAE	5	17.2	5.8-35.8
TEAE Resulting in Treatment Discontinuation	2[1]	6.9	0.8-22.8
Resulting in Death on Study	0	0.0	0.0-11.9

[1] One subject discontinued due to gastroenteritis which is reported in the MedDRA SOC of Infections and Infestations but was likely a GI AE related to lomitapide.

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).

Preventability:

Appropriate control of the fat intake in the diet is essential to improve the GI tolerability of lomitapide. Subjects should be placed on a low- fat diet defined as supplying less than 20% energy from fat prior to initiating Lojuxta treatment and should continue this diet during treatment.

A controlled diet should also mitigate the risk of weight loss, which may accompany lomitapide-induced diarrhoea. The reduction in body weight observed at the end of clinical studies did not exceed 2%.

Lomitapide may also impair the absorption of fat-soluble vitamins and cause a decline in essential fatty acids. These effects should be counterbalanced by the concomitant intake of dietary supplements. The SmPC states that 'patients should take daily dietary supplements that provide 400 IU vitamin E for adults and children aged 9 years and older or 200 IU vitamin E for children aged 5 to 8 years, 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.

In addition to the SmPC, information will be provided in the educational materials for prescribers and patients.

Compliance with the supplementation regimen will be assessed in the observational registry and the educational material amended if deemed necessary.

Section 4.4 of the SmPC states:

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.

Section 4.8 of the SmPC provides information on the frequency of gastro-intestinal effects of diarrhoea, nausea, vomiting and dehydration etc.

Impact on the risk-benefit balance of the product:

Vomiting is the main complication of nausea and may lead to symptomatic dehydration and electrolyte abnormalities in severe cases (Greenberger, 2008 The Merck Manual for Health Care Professionals). Chronic vomiting can result in undernutrition, weight loss and metabolic abnormalities. Similarly, diarrhoea may also induce dehydration and electrolyte abnormalities (Bharucha, 2007 The Merck Manual for Health Care Professionals).

Diarrhoea may vary in severity. Severe diarrhoea may also lead in some cases to dehydration.

The malabsorption of fat-soluble vitamins may result in various complications, including night blindness (vitamin A), bruising or bleeding (vitamin K) and pathologic fractures (vitamin D) (Ruiz, 2008 The Merck Manual for Health Care Professionals).

Essential fatty acid deficiency can cause an array of symptoms in virtually all organs of the human body, including skin rashes, decreased haematopoiesis, pulmonary complications, increased susceptibility to infections and hepatic steatosis (Yamanaka, 1980 Prog Lipid Res).

Public health impact:

The potential public health impact of this safety concern is not expected to be high. No serious AEs related to lomitapide GI effects were observed during clinical trials. Furthermore, the SmPC provides a number of recommendations (diet adjustments, intake of dietary supplements) that should significantly

contain this risk. In addition, subjects will be treated by specialised lipid experts where access to nutritional advice from dieticians is expected.

Important Identified Risk: Rhabdomyolysis with or without acute renal failure due to interaction with statins

Potential mechanisms:

The impact of steady-state dosing of 10 mg and/or 60 mg of lomitapide on the single-dose PK parameters of the main statins used in clinical practice was evaluated. The combination of lomitapide with atorvastatin and rosuvastatin results in either no change or very modest changes in the PK parameters of both statins at lomitapide doses up to 60 mg. By contrast, simvastatin levels increased by a factor of 2 when co-administered with lomitapide 60 mg.

Evidence source(s) and strength of evidence:

Clinical Study: 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 in adults. Because 27 of the 29 patients in the Phase 3 study were on statins, the influence of concomitant statins on hepatic AEs is unknown.

Overall, 5 subjects (11.6%) were reported with TEAEs in the SOC musculoskeletal and connective tissue disorders, all aged 11 to 17 years in the APH-19 paediatric study. Arthralgia was reported for 2 subjects, and exostosis, myalgia, and tendon disorder were reported for 1 subject each. The TEAE of myalgia (Subject 03/01, Day 251) was mild, unrelated to study drug, and resolved without treatment or dose change after 6 days. The subject was taking ezetimibe (10 mg QD) and atorvastatin (80 mg QD). This subject did not experience an increase of CK during the study.

Post-marketing experience: Cumulatively up to 31 July 2024, there were 2 spontaneous cases of potential interaction between lomitapide and statins. The first case reported a non-serious event of Liver function test increased. The second case reported a non-serious event of Low density lipoprotein increased. No cases cumulatively reported rhabdomyolysis due to an interaction with statins.

Characterisation of the risk:

When lomitapide 60 mg was administered to steady state prior to simvastatin 40 mg, simvastatin acid AUC and Cmax increased 68% and 57%, respectively. When lomitapide 60 mg was administered to steady state prior to atorvastatin 20 mg, atorvastatin acid AUC and Cmax increased 53% and 63%, respectively. When lomitapide 60 mg was administered to steady state prior to rosuvastatin 20 mg, which is primarily metabolised by CYP 2C9, rosuvastatin Tmax increased from 1 to 4 hours and its Cmax was unchanged.

The interaction between lomitapide and simvastatin and atorvastatin is due to the competition for CYP3A4 metabolism. The result of this concomitant use may be an increased availability of statins, with a consequent higher probability of adverse reactions related to these medications.

Myopathies and hepatic injury are the two main safety concerns related to high doses of statins. Myopathies generally occur rarely (≥ 1/10000, < 1/1000) in patients treated with simvastatin, although the frequency tends to increase with higher doses. Hepatic injuries are also rare or very rare occurrences (<1/1000 overall) in patients taking simvastatin (Simvador, 2010 Summary of Product Characteristics).

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 ischemia, 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.

Preventability:

The consequences of this interaction are fully addressed in the SmPC. The use of Lojuxta with doses of simvastatin (>40 mg) is contraindicated (Section 4.3 of the SmPC).

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 (Section 4.4 of the SmPC).

Information on this risk will also be provided in educational materials for prescribers and patients.

Impact on the risk-benefit balance of the product:

Rhabdomyolysis presents initially with muscle pain, tenderness or weakness. If left unrecognised and untreated, it may lead to renal failure and potential fatality.

The impact on individual patient liver disease are discussed under "Identified Risk: Hepatic events" in this Module VII.

Public health impact:

The drug interaction studies conducted by Aegerion (the previous MAH) support the potential for broad combination use of lomitapide in HoFH treated with statins. However, rare but serious consequences (rhabdomyolysis, hepatic injury) due to the increased availability of HMG-CoA reductase inhibitors cannot be excluded.

Important Potential Risk: Hepatic fibrosis

Potential mechanisms:

Lomitapide effects on the liver (i.e. hepatic enzyme elevation and steatosis) may be the consequence of MTP inhibition, which blocks triglyceride transfer to VLDL (the precursor of LDL) (Joy, 2008 Nat Clin Pract Cardiovasc Med). Chronic liver disease may eventually cause fibrosis, which is the result of the wound-healing response of the liver to repeated injury (Bataller, 2005 J Clin Invest).

Evidence source(s) and strength of evidence:

Clinical Study: No cases of hepatic fibrosis were observed in CTs with lomitapide.

Post-marketing experience: Cumulatively, up to 31 July 2024, were 4 cases of serious Hepatic fibrosis.

Characterisation of the risk:

It has been estimated that hepatic fibrosis affects more than 10 million people worldwide (Balsano, 2009 Curr Drug Targets). However, the real prevalence is likely to be higher, because hepatic fibrosis remains asymptomatic for many years and is probably undetected in many cases. In Canada, an autopsy series of lean individuals showed a 7% prevalence of liver fibrosis (Vernon, 2011 Aliment Pharmacol Ther). Similar figures have been reported in the US (Clark, 2006 J Clin Gastroenterol). Non-alcoholic fatty liver disease is a chronic liver disease often associated with fibrosis: it is found in 6-14% of adult individuals, and up to 47% of them have fibrosis (Clark, 2006 J Clin Gastroenterol).

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).

Preventability:

The requirement for monitoring of liver function is set out in the SmPC.

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.

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:

For paediatric patients:

- Imaging for hepatic fat content by ultrasound or NMR imaging / MRI
- Gamma-GT and serum albumin to detect possible liver injury

For adult patients:

- 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.

Impact on the risk-benefit balance of the product:

Hepatic fibrosis is asymptomatic but can lead to serious complications such as portal hypertension and cirrhosis (Shaffer, 2007 The Merck Manual for Healthcare Professionals).

Public health impact:

The progression to cirrhosis is usually slow and takes over 15-20 years in most instances (Bataller, 2005 J Clin Invest). Hepatic fibrosis can be treated by removing the primary cause of liver injury and appears to be reversible even when advanced (Bataller, 2005 J Clin Invest; Shaffer, 2007 The Merck Manual for Healthcare Professionals). Based on this evidence, the risk minimisations proposed by Chiesi should effectively prevent major health consequences in lomitapide users.

Important Potential Risk: Primary hepatic tumours

Potential mechanisms:

Since lomitapide did not show genotoxic potential, the increased incidence of liver tumours in a 2-year carcinogenicity study in mice is considered to be epigenetic (i.e., not secondary to direct DNA damage). Lipid vacuolation did not play a role in increasing tumour incidence. Indeed, this finding was also observed in the carcinogenicity study in rats, where the liver did not emerge as a target tissue for tumours. There were no other findings in the liver related to the tumours.

Evidence source(s) and strength of evidence:

Clinical Study: No cases of benign or malignant liver neoplasms were observed in CTs with lomitapide.

Post-marketing experience: Cumulatively, 2 cases reporting Primary hepatic tumour have been reported from the post marketing sources up to 31 Jul 2024. One serious solicited ICSR 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. Another serious solicited ICSR concerned an 81-year-old female patient who on an unspecified date, the patient was in the hospital with newly diagnosed liver and uterine cancer. Her physician recommended to stop taking lomitapide. The patient passed away. The reporter did not provide a causal relationship between the reported events and lomitapide. Due to limited information on the concomitant medications, complete medical history (including previous malignancies), duration of lomitapide treatment, details on circumstances surrounding the death of the patient, cause of death, concurrent conditions, relevant laboratory investigation reports, autopsy details, etc., it is not possible to make a conclusive assessment.

Characterisation of the risk:

There is no indication that FH patients have a higher risk of developing cancer than the general population. Treating this condition may actually decrease cancer incidence, as suggested by a large prospective registry study conducted in the UK (Neil, 2008 Eur Heart J). A total of 3,382 patients with heterozygous FH were followed for two long periods (from 1980 to 1992 and from 1992 to 2006), during which all causes of mortality were recorded. Interestingly, a 37% reduction in cancer mortality compared

to rates in the general population was calculated for the 1992-2006 observation period. The authors could not explain this phenomenon, although the influence of lifestyle changes (healthier diet, no smoking) probably played a role. The incidence rate of fatal cancers of digestive organs and peritoneum (no further details on cancer type were provided) was 0.54 per 1,000 person-years.

The incidence rates of all types of cancer within the EU are regularly provided by the European Cancer Observatory. For the year 2008, the incidence rate of hepatic cancer in all 27 EU countries was 6.7 per 100,000 persons (European Cancer Observatory, 2011). The mortality rate was 6.5 per 100,000. A higher incidence of hepatic cancer was observed in men (10.6 per 100,000) than in women (3.6 per 100,000).

Similar rates were observed in the US during the 2004-2008 period. The incidence rate of hepatic cancer (per 100,000) was 11.2 in men and 3.9 in women (National Cancer Institute, 2011b).

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).

Preventability:

Because the relevance of the hepatocellular tumours in mice for humans is unknown, it is not possible to speculate on preventative measures. However, it should be noted that this is the same situation for other marketed drugs associated with tumours in rodents for which tumorigenic mechanisms have not been established.

Impact on the risk-benefit balance of the product:

Hepatocellular carcinoma may be symptomless in the early stages and patients may present with symptoms when the condition is further advanced and treatment options limited leading to fatality.

Public health impact:

Statistical evidence indicates that over 75% of patients diagnosed with primary hepatocellular carcinoma die from this disease (European Cancer Observatory, 2011; National Cancer Institute, 2011b). The potential public health impact of this safety concern might therefore be high, although the relevance to humans of the non-clinical data collected in mice is unknown.

Important Potential Risk: Small intestinal tumours

Potential mechanisms:

Since lomitapide did not show genotoxic potential, the increased incidence of small intestine tumours in a 2-year carcinogenicity study in mice is considered to be epigenetic (i.e., not secondary to direct DNA damage). No relationship was noted with lipid vacuolation in the small intestine, which was reversible, generally dose-dependent and considered a secondary result of the pharmacodynamic effect of lomitapide. In addition, there were no other findings in the small intestine related to the tumours.

Evidence source(s) and strength of evidence:

Clinical Study: No cases of benign or malignant intestinal neoplasms were observed in Clinical Studies.

Post-marketing experience: One case reporting a small intestine carcinoma was identified up to 31 July 2024. 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.

Characterisation of the risk:

In spite of constituting 90% of the mucosal surface area of the GI tract, the small intestine is the site of <5% of all GI malignancies (Howdle, 2003 QJM).

US data for the period 2004-2008 show that the age-adjusted incidence rate was 2.0 per 100,000 men and women per year. There is a slightly higher incidence of small intestinal cancer in men (2.4 per 100,000) than in women (1.6 per 100,000) (European Cancer Observatory, 2012).

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).

Preventability:

Because the relevance of the small intestine tumours in mice for humans is unknown, it is not possible to speculate on preventative measures other than those aimed to contain the general risk factors for small intestinal cancer (e.g., avoiding high fat diets). However, it should be noted that this is the same situation for other marketed drugs associated with tumours in rodents for which tumorigenic mechanisms have not been established.

Impact on the risk-benefit balance of the product:

Patients may initially present with non-specific gastro-intestinal symptoms. Early investigation of such symptoms is required in order to identify the condition at an early stage to allow for potential treatment options.

Public health impact:

Statistical evidence indicates that approximately 15% of patients diagnosed with small intestinal cancer die from this disease (National Cancer Institute, 2011b). The potential public health impact of this safety concern might therefore be high, although the relevance to humans of the non-clinical data collected in mice is unknown.

Important Potential Risk: Pancreatic tumours

Potential mechanisms:

Lomitapide did not show genotoxic potential. Hence the non-statistically significant increase in tumour incidence in male rats (up to 99 weeks of administration at 7.5 mg/kg/day) is considered to be epigenetic (i.e., not secondary to direct DNA damage). Although lipid vacuolation occurred in the acinar pancreas, there was no correlation with rats that developed pancreatic tumours. Further, females had a much higher incidence of lipid vacuolation in the acinar pancreas (i.e., approximately 4.5 times higher than the highest incidence in males) but did not develop pancreatic tumours.

Evidence source(s) and strength of evidence:

Clinical Study: No cases of benign or malignant pancreatic neoplasms were observed in clinical studies.

Post-marketing experience: One case of Primary pancreatic tumour was identified up to 31 July 2024. 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. Note, this is the same case described in Hepatic Tumours.

Characterisation of the risk:

About 68,000 new cases of pancreatic cancer are diagnosed each year in the European Union, making it the 10th most frequent type of cancer. About 1 in every 100 European men and 1 in every 150 European women will develop pancreatic cancer at some point in their life (European Cancer Observatory, 2012). In the US, the lifetime risk of developing pancreatic cancer is about 1 in 78 (American Cancer Society, 2013).

Data collected in 2012 from all 27 EU countries showed an incidence rate of 10.5 per 100,000 persons for both sexes (European Cancer Observatory, 2012). The mortality rate was 10.1 per 100,000.

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).

Preventability:

Because the relevance of the pancreatic tumours in rats for humans is unknown, it is not possible to speculate on preventative measures other than those aimed to contain the general risk factors for pancreatic cancer. However, it should be noted that this is the same situation for other marketed drugs associated with tumours in rodents for which tumorigenic mechanisms have not been established.

Impact on the risk-benefit balance of the product:

As the majority of cases are diagnosed in the advanced stages, curative therapy is nearly impossible and mortality equals incidence (Hariharan, 2008 HPB (Oxford)).
Public health impact:

Pancreatic cancer is the fourth most common cause of cancer-related death in the Western world (Hariharan, 2008 HPB (Oxford)).

The potential public health impact of this safety concern might be high, although the relevance to humans of the non-clinical data collected in rats is unknown.

Important Potential Risk: Unintended pregnancy

Potential mechanisms:

Lomitapide MTP inhibition causes triglyceride accumulation not only in the liver but also in the intestine. Presumably, diarrhoea develops as a consequence of this mechanism of action (Samaha, 2008 Nat Clin Pract Cardiovasc Med). The reduced bowel transit time may affect the absorption of concomitant oral contraceptives.

Evidence source(s) and strength of evidence:

There were no reports of unintended pregnancy in the adult and paediatric clinical development programme. In the post-marketing setting up to 31 July 2024, there were 18 pregnancies reported in total with 5 reports of non-serious cases of unintended pregnancy, one ICSR was terminated via abortion due to social reasons, and the other 4 ICSRs resulted in healthy infants. Of the remaining 13 pregnancies, there were 7 live births of babies with no birth defects (however one concerned the live birth of a premature infant who developed fatal nosocomial infection which was not related to lomitapide) and 1 spontaneous abortion assessed as not related to lomitapide, and 5 unknown pregnancy outcomes.

Characterisation of the risk:

No cases of unintended pregnancy were identified in adult and paediatric clinical trials with lomitapide. There have been 18 reports of pregnancy up to 31 July 2024, five of which were unintended pregnancy among which all were non-serious cases, 1 ICSR was terminated via abortion due to social reasons, and the other 4 ICSRs resulted in healthy infants.

Of the remaining 13 pregnancies, there were 7 reports of live births of babies with no birth defects (however one concerned the live birth of a premature infant who developed fatal nosocomial infection which was not related to lomitapide) and 1 spontaneous abortion assessed as not related to lomitapide, and 5 unknown outcomes.

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.

Preventability:

As reported in Section 4.4 of the SmPC, ‘before initiating treatment in women and adolescents 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. Oestrogen containing oral contraceptives are weak CYP3A4 inhibitors.

This warning is also in place in Section 4.6 of the SmPC.

In Section 4.5 of the SmPC the warning is repeated. Oral contraceptives: When lomitapide 50 mg was administered to steady state along with an oestrogen based oral contraceptive, no clinically meaningful nor statistically significant impact on the pharmacokinetics of the components of the oral contraceptive (EE and 17 deacetyl norgestimate, the metabolite of norgestimate) were 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.

In this regard, appropriate control of the fat intake in the diet is essential to reduce the likelihood of diarrhoea and vomiting. Patients should follow a diet supplying less than 20% of energy from fat prior to initiating lomitapide treatment, and should continue this diet during treatment. Dietary counselling should be provided. Additionally, a gradual dose escalation is recommended in order to minimise GI adverse effects (see SmPC, Section 4.2).

Educational materials for prescribers and for patients also provide the same advice.

Impact on the risk-benefit balance of the product:

Unintended pregnancy may have a major medical, psychological, social and financial impact on a patient.

Public health impact:

Lomitapide proved to be teratogenic in non-clinical studies and therefore is contraindicated in pregnancy. Importantly, a pharmacokinetic study investigating the co-administration of lomitapide 50 mg with an oestrogen-based oral contraceptive for 8 days revealed no clinical or statistically significant impact on the pharmacokinetics of the components of the oral contraceptive (ethinyl oestradiol and 17-deacetyl norgestimate, the metabolite of norgestimate). This suggests that lomitapide should have no impact on the efficacy of oestrogen-based oral contraceptives. Furthermore, the preventive actions proposed in the SmPC (see above) should minimise the risk of possible malabsorption of oral contraceptives due to diarrhoea and/or vomiting.

SVII.3.2 Presentation of the missing information

Missing Information: Use during pregnancy

Evidence source: No cases of unintended pregnancy were identified in adult and paediatric clinical trials with lomitapide. There have been 18 reports of pregnancy up to 31 July 2024, five of which were unintended pregnancy, one ICSR was terminated via abortion due to social reasons, and the other 4 ICSRs resulted in healthy infants.

Of the remaining 1*3 pregnancies, there were 7 reports of live births of babies with no birth defects (however one concerned the live birth of a premature infant who developed fatal nosocomial infection which was not related to lomitapide) and 1 spontaneous abortion assessed as not related to lomitapide, and 5 unknown outcomes.*

Population in need of further characterisation:

The risks of use in pregnancy cannot be defined based on available data and thus the safety profile in this population will be derived from routine and additional pharmacovigilance activities.

Anticipated risk/consequence of the missing information:

If the drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the potential hazard to the fetus must be considered. Because studies are not able to rule out the possibility of harm, the following are considered anticipated risks: congenital malformation, other neonatal outcomes, such as prematurity, low birth weight, abnormal neurodevelopment, functional abnormalities, miscarriage, and stillbirth.

Missing Information: Long term safety in children

Evidence source:

The safety profile of lomitapide in children < 5 years has not been established from the current clinical development programme and long term safety data in children has not been established.

Population in need of further characterisation:

The risks of use in the paediatric population (less than 5 years) cannot be defined based on available data and thus the safety profile in this population will be derived from routine and additional pharmacovigilance activities. A Paediatric Investigation Plan (PIP) was agreed. A benefit risk/assessment focused on paediatric use has been carried out by the PDCO and a study evaluating the efficacy and long-term safety in paediatrics has been completed. From the real world experience of lomitapide use in a case series of 11 paediatric patients with HoFH, the safety profile of the medication was similar to that of the use in adult patients with the disease. The completed APH-19 trial confirmed the same.

Anticipated risk/consequence of the missing information:

Based on the current product knowledge from real world/ post marketing data, no entirely new risks are anticipated in paediatric population. Based on the completed APH-19 paediatric study, the safety profile of lomitapide in paediatric subjects revealed no new safety signals compared to adult patients with HoFH. The most frequently reported side effects were transient gastrointestinal disorders or hepatic abnormalities that resolved with dose reduction, suspension or watchful waiting. Gastrointestinal events were less frequent and less severe in paediatric patients. Hepatic fat accumulation was mild and consistent with published evidence for adults. Growth and development of the children was not adversely impacted by treatment with lomitapide.

Missing Information: Use with alcohol

Evidence source:

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

Population in need of further characterisation:

As a precautionary measure, patients with history of alcohol use or alcohol abuse were excluded from the inclusion under clinical studies. The risk of hepatic injury can be aggravated with the use of alcohol in patients on lomitapide therapy. Owing to the hepatotoxicity potential of alcohol which is directly proportional to the amount of alcohol consumed and duration of consumption. Therefore, it is anticipated concurrent alcohol consumption while on lomitapide therapy may increase fat accumulation in liver resulting in liver injury inducement or exacerbation and steatohepatitis.

Anticipated risk/consequence of the missing information:

Because it is not possible to rule out the inducement and/ or exacerbation of hepatic injury in patients on lomitapide therapy, the use of alcohol during lomitapide treatment is not recommended.

Missing Information: Use in non-Caucasian patients

Evidence source:

Majority of HoFH patients studied under clinical development are of Caucasian, and only small group of non-Caucasian ethnicity were studied.

Population in need of further characterisation:

In the clinical development programme, 86% of the patients with HoFH were of Caucasian origin, and data suggestive of No dose adjustment is required for Caucasian or Latino patients.

Anticipated risk/consequence of the missing information:

There is insufficient information to determine if lomitapide requires dose adjustment in non-Caucasian races considering the genetic variability. 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.

Missing Information: Pre-existing hepatic disease

Evidence source:

Lojuxta has been studied 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.

Population in need of further characterisation:

Lojuxta has not been studied in patients with severe hepatic impairment. By means of MTP inhibition, the medication may induce or exacerbate the accumulation of fat and triglycerides in liver and in turn resulting in further potentiation pre-existing hepatic disorder.

Anticipated risk/consequence of the missing information:

Owing to the anticipated risk of lomitapide use, Lojuxta is contraindicated in patients with moderate or severe hepatic impairment including patients with unexplained persistent abnormal liver function tests.

Missing Information: Concomitant use with potential hepatotoxic agents

Evidence source:

The patient population may need therapy involving other medications which may be of potential hepatotoxins. It is well known that the manifestations of drug induced hepatotoxicity are highly variable, ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure.

Population in need of further characterisation:

Patients taking concomitant hepatotoxic agents were excluded from the clinical trial programme. The risk of hepatic injury may be aggravated with the concomitant use of potential hepatotoxic medications in patients under lomitapide therapy.

Anticipated risk/consequence of the missing information:

Because it is not possible to rule out the inducement and/ or exacerbation of hepatic injury in patients on lomitapide therapy, the concomitant use of other hepatotoxic agents during lomitapide treatment is not recommended.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Summary of safety concerns

Table 11: Summary of safety concerns

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 Long-term safety in children Use with alcohol Use in non-Caucasian patients Pre-existing hepatic disease Concomitant use with potential hepatotoxic agents

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse drug reactions reporting and signal detection:

Specific adverse drug reaction follow-up questionnaires for: Hepatic effects, fibrosis and tumours

Objectives

The use of specialised query report follow up forms to enhance data quality. The review of each relevant case to allow an assessment of causality, aetiology, and risk factors. Aggregate analysis and regular signal detection activities to allow for the identification of trends and any change to the benefit-risk profile.

Forms

The specialised query follow up forms are:

- elevations of hepatic transaminases resulting in discontinuation of lomitapide
- elevations of hepatic transaminases >3 x ULN that persist despite dose reduction or interruption
- elevations of hepatic transaminases ≥5 x ULN
- symptomatic liver injury
- other hepatic evaluation and testing or any histology obtained from liver biopsy and imaging evaluations.

Specific adverse reaction follow-up questionnaires for: Gastrointestinal effects

Objectives

The use of specialised query report follow up forms to enhance data quality. The review of each relevant case to allow an assessment of causality, aetiology, and risk factors. Aggregate analysis and regular signal detection activities to allow for the identification of trends and any change to the benefit-risk profile.

Forms

The specialised query follow up forms are:

- events leading to permanent treatment discontinuations
- hospitalisation due to gastrointestinal events
- events triggering additional investigations such as endoscopy

Specific adverse reaction follow-up questionnaires for: Tumours

Objectives

The use of specialised query report follow up forms to enhance data quality. The review of each relevant case to allow an assessment of causality, aetiology, and risk factors. Aggregate analysis and regular signal detection activities to allow for the identification of trends and any change to the benefit-risk profile.

Forms

The specialised query follow up forms are:

- small bowel tumours
- intestinal tumours
- pancreatic tumours

Specific adverse reaction follow-up questionnaires for: Use during pregnancy/Paediatric outcomes

Objectives

The use of specialised query report follow up forms to enhance data quality. The review of each relevant case to allow an assessment of causality, aetiology, and risk factors. Aggregate analysis and regular signal detection activities to allow for the identification of trends and any change to the benefit-risk profile.

Forms

The specialised query follow up forms are:

- use during pregnancy / unintended pregnancy (maternal and paternal exposure)
- paediatric outcome

Other forms of routine pharmacovigilance activities

Adverse events of special interest

Enhanced Pharmacovigilance will include systematically collecting and reviewing the Adverse Events of Special Interest (AESI) including:

- Hepatic, small bowel / intestinal, pancreatic and colorectal* tumours
- Hepatic abnormalities
    - elevations of hepatic transaminases resulting in discontinuation of lomitapide
    - elevations of hepatic transaminases >3 x ULN that persist despite dose reduction or interruption
    - elevations of hepatic transaminases ≥5 x ULN
    - symptomatic liver injury
    - other hepatic evaluation and testing or any histology obtained from liver biopsy and imaging evaluations
- Gastrointestinal effects
    - events leading to permanent treatment discontinuations
    - hospitalisation due to gastrointestinal events
    - events triggering additional investigations such as endoscopy
- Major congenital anomalies

In addition to reporting the AESIs within 15 calendar days, they will be discussed in relevant safety aggregate reports.

The AESIs will also be diligently followed up with the relevant reporters using specialized query follow up forms and they will be also be identified as potential signals that will be reviewed during routine monthly signal detection activities.

*Colorectal tumours will be considered to be Adverse Events of Special Interest (AESI) in the observational registry of patients treated with lomitapide, and therefore will be included in enhanced pharmacovigilance activities.

III.2 Additional pharmacovigilance activities

Annual safety and efficacy report: In order to ensure adequate monitoring of safety and efficacy of Lojuxta in the treatment of patients with homozygous familial hypercholesterolaemia (HoFH), the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Lojuxta.

An annual report will be submitted yearly, simultaneously with submission of Periodic Safety Update reports.

III.3 Summary Table of additional Pharmacovigilance activities

Table 12 On-going and planned additional pharmacovigilance activities

DESCRIPTION	DUE DATES
CATEGORY 2– IMPOSED MANDATORY ADDITIONAL PHARMACOVIGILANCE ACTIVITIES WHICH ARE SPECIFIC OBLIGATIONS IN THE CONTEXT OF A CONDITIONAL MARKETING AUTHORISATION OR A MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES	
Annual safety and efficacy report: In order to ensure adequate monitoring of safety and efficacy of Lojuxta in the treatment of patients with homozygous familial hypercholesterolaemia (HoFH), the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Lojuxta.	An annual report will be submitted yearly, simultaneously with submission of Periodic Safety Update reports.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

IV.1 Applicability of Efficacy to All Patients in the Target Population

Due to the rarity of the disease, a single major efficacy and safety study was conducted in patients with HoFH, which was a single arm, open label study in 29 patients. Including the dose escalation study, 35 patients with HoFH have been exposed to lomitapide in clinical trials. In the Phase 3 study UP 1002/AERG-733-005, patients were treated for a total of 78 weeks. There is therefore a need to study the efficacy of lomitapide in a larger patient population and for a long duration. The LOWER study evaluated the long-term effectiveness of lomitapide in maintaining control of serum lipid levels in clinical practice.

In the Phase 3 study UP 1002/AERG-733-005, lomitapide demonstrated marked reductions in LDL-C and other atherogenic lipoproteins. Patients with HoFH have very significant atheroma burden resulting in premature vascular atheromatous disease. A multi-centre, open label retrospective and prospective

study will explore the occurrence of Major Adverse Cardiovascular Events (MACE) in patients with HoFH on lomitapide therapy.

IV.2 Tables of Post-authorisation Efficacy Studies

Table 13 Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

STUDY STATUS	SUMMARY OF OBJECTIVES	EFFICACY UNCERTAINTIES ADDRESSED	MILESTONES	DUE DATE
Evaluation of the effect of lomitapide treatment on major adverse cardiovascular event (MACE) in patients with homozygous familial hypercholesterolaemia (HoFH). (LILITH study) Ongoing	**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).	Assess changes in the occurrence of MACE from pre to post lomitapide initiation	Protocol Final report	22 Jun 2023 30 Jun 2027

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1 Routine Risk Minimisation Measures

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

Table 14 Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
Hepatic effects (elevated aminotransferases, hepatic steatosis)	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.
Gastrointestinal effects (nausea, diarrhoea, weight loss, malabsorption of fat soluble vitamins, decline in essential fatty acids)	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.
Rhabdomyolysis with or without acute renal failure due to interaction with statins	Routine risk communication • SmPC section 4.3. Routine risk minimisation activities recommending specific clinical measures to address the risk: • 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.

Hepatic fibrosis	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.
Primary hepatic tumours	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.
Small bowel / intestinal tumours	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.
Pancreatic tumours	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.
Unintended pregnancy	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.

Use during pregnancy	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.
Long-term safety in children	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.
Use with alcohol	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.
Use in non-Caucasian patients	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.
Pre-existing hepatic disease	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.

Concomitant use with potential hepatotoxic agents	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.

V.2 Additional Risk Minimisation Measures

Educational material for prescribers

Objectives:

The educational material aims to ensure that HCPs understand the risk of the following:

- hepatotoxicity (including hepatic fibrosis, use in patients with pre-existing hepatic disease and concomitant use with hepatotoxic agents)
- gastro-intestinal risks
- potential for risk of rhabdomyolysis with or without acute renal failure due to interaction with statins
- hepatic fibrosis
- use in patients with pre-existing hepatic disease
- concomitant use with hepatotoxic agents
- the possible loss of effectiveness of oral contraceptives due to diarrhoea or vomiting and the need for additional contraception for 7 days after symptoms have resolved
- teratogenesis and thus is contraindicated in pregnancy
- that alcohol has the potential to induce or exacerbate liver injury and should not be used by patients taking lomitapide
- that caution should be exercised when Lojuxta is coadministered with potential hepatotoxic agents
- the need for specific screening at baseline and annually

Rationale for the additional risk minimisation activity

The educational material aims to:

a) foster understanding of the above risks associated with Lojuxta;

b) emphasize that Lojuxta is contraindicated in adult and paediatric patients with moderate or severe hepatic impairment, patients with unexplained persistent abnormal liver function tests, patients with a known significant or chronic bowel disease such as inflammatory bowel disease or malabsorption; those who are pregnant.

These materials also provide information regarding the mandated registry to encourage all prescribers to enrol all patients. They also ensure HCPs are aware of the risks of Lojuxta and are able to monitor and adjust the treatment accordingly

Target audience and planned distribution path:

Educational materials are available for potential prescribers of Lojuxta. These are made available through personal mailing, field company personnel, and the company website.

Plans to evaluate the effectiveness of the interventions and criteria for success

Not applicable

Educational material for patients

Objectives:

Educational materials are provided to patients to provide information and advice on and how to minimise the risks of:

- hepatotoxicity (how to minimise these and the need for regular blood and liver related tests)
- gastro-intestinal risks, on following a diet that supplies less than 20% of energy from fat, on the need to take Lojuxta at bedtime with a glass of water and without food
- risk of rhabdomyolysis with or without acute renal failure due to interaction with statins
- possible loss of effectiveness of oral contraceptives due to diarrhoea or vomiting and the need for additional contraception for 7 days after symptoms have resolved
- teratogenesis and thus is contraindicated in pregnancy
- that alcohol has the potential to induce or exacerbate liver injury and should not be used by patients taking lomitapide
- that caution should be exercised when Lojuxta is coadministered with potential hepatotoxic agents

Rationale for the additional risk minimisation activity

The educational material aims to:

a) foster understanding of the above risks associated with Lojuxta;
b) emphasize that Lojuxta is contraindicated in patients with moderate or severe hepatic impairment, patients with unexplained persistent abnormal liver function tests, patients with a known significant or chronic bowel disease such as inflammatory bowel disease or malabsorption; those who are pregnant.

Patients are provided with a “patient alert card” and are instructed to carry this with them at all times. The purpose of this card is to inform any other treating healthcare professional of the potential of interactions with other medicinal products.

Target audience and planned distribution path:

Chiesi has prepared educational materials and the “patient alert card” for patients. The materials are available to prescribers who can then use the materials for patient counselling and can provide copies to patients directly at the time Lojuxta treatment is initiated. This information is provided in clear, lay language that should be easily grasped by any patient.

Plans to evaluate the effectiveness of the interventions and criteria for success

Not applicable.

V.3 Summary of risk minimisation measures

Table 15 Summary table of pharmacovigilance activities and risk minimization measures by safety concern

Important identified risks

Safety Concern	Risk minimisation measures	Pharmacovigilance activities
Hepatic effects (elevated aminotransferases, hepatic steatosis)	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. Educational material for prescribers and patients.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AESI Follow-up Questionnaire. **Additional pharmacovigilance activities:** Annual safety and efficacy report

Safety Concern	Risk minimisation measures	Pharmacovigilance activities
Gastrointestinal effects (nausea, diarrhoea, weight loss, malabsorption of fat-soluble vitamins, decline in essential fatty acids)	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. Educational material for prescribers and patients.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AESI Follow-Up Questionnaire. **Additional pharmacovigilance activities:** Annual safety and efficacy report
Rhabdomyolysis with or without acute renal failure due to interaction with statins	Routine risk communication • SmPC section 4.3. Routine risk minimisation activities recommending specific clinical measures to address the risk: • 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. Educational material for prescribers and patients.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Annual safety and efficacy report

Important potential risks

Safety Concern	Risk minimisation measures	Pharmacovigilance activities
Hepatic fibrosis	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. Educational material for prescribers and patients.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AESI Follow-up Questionnaire. **Additional pharmacovigilance activities:** Annual safety and efficacy report
Primary hepatic tumours	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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AESI Follow-up Questionnaire. **Additional pharmacovigilance activities:** Annual safety and efficacy report
Small bowel / intestinal tumours	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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AESI Follow-up Questionnaire. **Additional pharmacovigilance activities:** Annual safety and efficacy report

Safety Concern	Risk minimisation measures	Pharmacovigilance activities
Pancreatic tumours	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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AESI Follow-up Questionnaire. **Additional pharmacovigilance activities:** Annual safety and efficacy report
Unintended pregnancy	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. Educational material for prescribers and patients.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AESI Follow-up Questionnaire. **Additional pharmacovigilance activities:** Annual safety and efficacy report

Important missing information

Safety Concern	Risk minimisation measures	Pharmacovigilance activities
Use during pregnancy	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. Educational material for prescribers and patients.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: AESI Follow-up Questionnaire. **Additional pharmacovigilance activities:** Annual safety and efficacy report
Long-term safety in children	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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Annual safety and efficacy report

Safety Concern	Risk minimisation measures	Pharmacovigilance activities
Use with alcohol	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. Educational material for prescribers and patients.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Annual safety and efficacy report
Use in non-Caucasian patients	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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Annual safety and efficacy report
Pre-existing hepatic disease	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. Educational material for prescribers and patients.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Annual safety and efficacy report

Safety Concern	Risk minimisation measures	Pharmacovigilance activities
Concomitant use with potential hepatotoxic agents	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. Educational material for prescribers and patients.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Annual safety and efficacy report

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 and paediatric patients aged 5 years and older 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 Long-term safety in children 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. There have been no cases of acute hepatotoxicity (i.e., cases that met Hy's law criteria) observed in the lomitapide adult 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. The most frequently reported side effects were hepatic abnormalities in the paediatric APH-19 study that resolved with dose reduction or suspension. Hepatic TEAEs were reported for 23 (53.5%) subjects overall, with similar frequency in the 2 age groups (5 to 10 years and 11 to 17 years). The most frequently reported hepatic TEAEs were ALT increased and AST increased, reported for 39.5% and 34.9% of subjects, respectively. Hepatic fat accumulation was mild and consistent with published evidence for adults. No cases of Hy's law or severe hepatic dysfunction (e.g., hyperbilirubinemia) were observed, indicating that the hepatic effects associated with lomitapide were primarily asymptomatic and reversible. Across the lomitapide programme, 6 studies included an evaluation of hepatic fat. Review of scatter plots across these 6 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 July 2024, there were 612 ICSRs (450 solicited, 134 spontaneous, 28 literature) reporting 902 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).

Important identified risk: Hepatic effects	
	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 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. As 27 of the 29 patients in the adult Phase 3 study and 39 of the 43 subjects in the paediatric 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.

Important identified risk: Hepatic effects	
	Educational material for prescribers and patients.
Additional pharmacovigilance activities	Annual safety and efficacy report

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. In the adult 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 APH-19 study, Treatment emergent adverse events in the SOC of Gastrointestinal disorders were reported by 72.1% of subjects with slightly lower incidence in subjects 5 to 10 years (65.0% of subjects) than 11 to 17 years (78.3% of subjects). In the post-marketing setting, cumulatively, through 31 July 2024, there were 1909 ICSRs (1379 solicited, 509 spontaneous, 21 literature) reporting 3492 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.

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

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 Adult Phase 3 study were on statins, the influence of concomitant statins on hepatic AEs is unknown. Overall, 5 subjects (11.6%) were reported with TEAEs in the SOC musculoskeletal and connective tissue disorders, all aged 11 to 17 years in the APH-19 paediatric study. Arthralgia was reported for 2 subjects, and exostosis, myalgia, and tendon disorder were reported for 1 subject each. The TEAE of myalgia (Subject 03/01, Day 251) was mild, unrelated to study drug, and resolved without treatment or dose change after 6 days. The subject was taking ezetimibe (10 mg QD) and atorvastatin (80 mg QD). This subject did not experience an increase of CK during the study. In the post-marketing setting, cumulatively up to 31 July 2024, there were 2 spontaneous cases of potential interaction between lomitapide and statins. The first case reported a non-serious event of Liver function test increased. The second case reported a non-serious event of Low density lipoprotein increased. No cases cumulatively reported rhabdomyolysis due to an interaction with statins.

Important identified risk: Rhabdomyolysis with or without acute renal failure due to interaction with statins	
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: • 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. Educational material for prescribers and patients.
Additional pharmacovigilance activities	Annual safety and efficacy report

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 July 2024, were 4 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:

Important potential risk: Hepatic fibrosis	
	• 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. Educational material for prescribers and patients.
Additional pharmacovigilance activities	Annual safety and efficacy report

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 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, 2 cases reporting Primary hepatic tumour have been reported from the post-marketing sources up to 31 July 2024. One serious solicited ICSR 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. Another serious solicited ICSR concerned an 81-year-old female patient who on an unspecified date, the patient was in the hospital with newly diagnosed liver and uterine cancer. Her physician recommended to stop taking lomitapide. The patient passed away. The reporter did not provide a causal relationship between the reported events and lomitapide. Due to limited information on the concomitant medications, complete medical history (including previous malignancies), duration of lomitapide treatment, details on circumstances surrounding the death of the patient, cause of death, concurrent conditions, relevant laboratory investigation reports, autopsy details, etc., it is not possible to make a conclusive assessment.
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

Important potential risk: Primary hepatic tumours	
	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	Annual safety and efficacy report

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. Post-marketing experience: One case reporting a small intestine carcinoma was identified up to 31 July 2024. 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.

Important potential risk: Small intestinal tumours	
	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	Annual safety and efficacy report

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 July 2024. 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. 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:

Important potential risk: Pancreatic tumours	
	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	Annual safety and efficacy report

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 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 July 2024, five of which were unintended pregnancy, 1 ICSR was terminated via abortion due to social reasons, and the other 4 ICSRs 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 In the Adult phase 3 Study UP1002/AEGR-733-005.
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.

Important potential risk: Unintended pregnancy	
	Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders. Educational material for prescribers and patients.
Additional pharmacovigilance activities	Annual safety and efficacy report

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. Educational material for prescribers and patients.
Additional pharmacovigilance activities	Annual safety and efficacy report

Missing information: Long-term safety in children	
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	Annual safety and efficacy report

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.

Missing information: Use with alcohol	
	Educational material for prescribers and patients.
Additional pharmacovigilance activities	Annual safety and efficacy report

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	Annual safety and efficacy report

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: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders. Educational material for prescribers and patients.
Additional pharmacovigilance activities	Annual safety and efficacy report

Missing information: Concomitant use with potential hepatotoxic 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.

Missing information: Concomitant use with potential hepatotoxic agents	
	Educational material for prescribers and patients.
Additional pharmacovigilance activities	Annual safety and efficacy report

II.C Post-authorisation development plan

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

Annual safety and efficacy report: In order to ensure adequate monitoring of safety and efficacy of Lojuxta in the treatment of patients with homozygous familial hypercholesterolaemia (HoFH), the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Lojuxta.

An annual report will be submitted yearly, simultaneously with submission of Periodic Safety Update reports.

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 hypercholesterolaemia (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.

Annex 4 Specific adverse drug reaction follow-up forms

AESI Follow-up forms:

Gastrointestinal events

Hepatic abnormalities

Malignancies

Pregnancy (including Maternal / Paternal Exposure)

Paediatric Outcome

All forms are available in the PDF copy and dossier.


Appendix E.k
Lomitapide Pediatric (


Appendix E.j
Lomitapide Pregnanc)


Appendix E.i
Lomitapide Malignan(


Appendix E.h
Lomitapide Hepatic Q


Appendix E.g
Lomitapide GI Events

Annex 6 Details of proposed additional risk minimisation activities

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 brochures
- Patient alert cards

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

- 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 and adolescents 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 for adults and children aged 9 years and older or 200 IU vitamin E for children aged 5 to 8 years, 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 medicinal products 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:
For paediatric patients:
- Imaging for hepatic fat content by ultrasound or NMR imaging
- Gamma-GT and serum albumin to detect possible liver injury

For adult patients:
- 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 and adolescents of childbearing potential

- That lomitapide was teratogenic in non-clinical studies and is contraindicated in women and adolescents 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 and adolescents 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 prescriber's 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.

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 lomitapide 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 medicines they are taking as special care should be taken

if other medicines 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 lomitapide was teratogenic in non-clinical studies and should not be taken during pregnancy or by patients trying to get pregnant;
- Women and adolescents 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;

Patient alert card

The purpose of the patient alert card is to inform health care professionals of potential drug-drug interactions before any additional medicinal product 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