NOVARTIS

Patient Safety & Pharmacovigilance

Inclisiran

KJX839

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Inclisiran
Product(s) concerned (brand name):	LEQVIO™
Document status:	Final
Version number:	3.1
Data lock point for this RMP	30-Jun-2023
Date of final sign off	25-Apr-2024

Rationale for submitting an updated RMP: This update to the European Union (EU) Risk Management Plan (RMP) is prepared in response to the PRAC assessment report (AR) with a Request for Supplementary Information (RSI), dated 11-Apr-2024, related to the submission of the final report of the clinical study ORION-8 via a type II variation (EMEA/H/C/005333/II/0021). As part of this RSI, the PRAC requested to delete the missing information of 'long-term safety' from the RMP safety specification and to update all relevant parts accordingly. This updated RMP reflects this request from the PRAC.

Summary of significant changes in this RMP:

- Update to reflect the deletion of missing information "long-term safety" from the RMP.

Part	Major changes compared to RMP v 3.0
Part I	No changes.
Part II	Module SVII and SVIII: Updated with deletion of missing information "long-term safety".
Part III	No changes.
Part IV	No changes.
Part V	Part V.1 and V.3: Updated with deletion of missing information "long-term safety".
Part VI	Part VI-II B: Updated with deletion of missing information "long-term safety".
Part VII	No changes done from Annex 1 to Annex 7 Annex 8: Updated to reflect the summary of changes made in this RMP version 3.1 update.

Other RMP versions under evaluation

No other RMP versions are currently under evaluation.

Details of the currently approved RMP:

Version number: 2.0

Approved with procedure: EMEA/H/C/005333/II/0013

Date of approval (CHMP Opinion date): 01-Sep-2022

QPPV name:

Dr. Justin Daniels, PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

Table of contents

List of tables

List of abbreviations

aPhV	Additional pharmacovigilance
AR	Assessment Report
ASCVD	Atherosclerotic Cardiovascular Disease
CSR	Clinical Study Report
DDD	Defined Daily Dose
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
HeFH	Heterozygous Familial Hypercholesterolemia
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
LDL-C	Low-Density Lipoprotein Cholesterol
LMP	Last menstrual period
MAH	Marketing Authorization Holder
PL	Patient Leaflet
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SAE	Serious adverse event
SCS	Summary of Clinical Safety
SOC	System organ class
SmPC	Summary of Product Characteristics

1 Part I: Product(s) Overview

Table 1-1 Part I.1 - Product Overview

Active substance(s) (INN or common name)	Inclisiran
Pharmacotherapeutic group(s) (ATC Code)	Other lipid modifying agents (C10AX16)
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	LEQVIO™
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Small interfering ribonucleic acid (siRNA)
	Summary of mode of action: Inclisiran is a cholesterol lowering double-stranded small interfering ribonucleic acid (siRNA), conjugated on the sense strand with triantennary N-acetylgalactosamine to facilitate uptake by hepatocytes. In hepatocytes, inclisiran utilizes the RNA interference mechanism and directs catalytic breakdown of messenger RNA for proprotein convertase subtilisin kexin type 9 (PCSK9). This increases low-density lipoprotein cholesterol (LDL-C) receptor recycling and expression on the hepatocyte cell surface, which increases LDL-C uptake and lowers LDL-C levels in the circulation.
	Important information about its composition: None of the excipients used are of human or animal origin. In addition, the primary container closure system does not pose a risk of transmitting spongiform animal encephalopathy agents.
Hyperlink to the Product Information	[Summary of Product Characteristics (SmPC)]
Indication(s) in the EEA	Current: Inclisiran is indicated in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet: - in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or, - alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.
Dosage in the EEA	Current: The recommended dose of inclisiran is 284 mg administered as a single subcutaneous injection: initially, again at 3 months followed by every 6 months.
Pharmaceutical form(s) and strengths	Current: Solution for injection. Solution is clear, colourless to pale yellow and essentially free of particulates. It is supplied in a pre-filled

	syringe in two presentations (with or without needle guard). Each pre-filled syringe contains inclisiran sodium equivalent to 284 mg inclisiran in 1.5 ml of solution.
Is/will the product be subject to additional monitoring in the EU?	Yes

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and disability worldwide and is expected to remain so beyond 2040 (Foreman et al 2018). After 30 years of progress, death rates associated with ASCVD may be increasing in the United States once more (Benjamin et al 2019).

Multiple factors contribute to the development of ASCVD. However, strong and consistent evidence from genetics, epidemiology, Mendelian randomisation studies, and randomised trials, establishes that among these factors, LDL-C is not merely a biomarker of increased risk, but a causal and modifiable factor in ASCVD (Ference et al 2017).

ASCVD is the leading cause of death among adults under the age of 75 years in Europe (Halcox et al 2017, McCormack et al 2016) with over 3.8 million deaths each year (Timmis et al 2017, Catapano et al 2016).

A large proportion of coronary heart disease (CHD) cases may be attributed to hyperlipidemia (Timmis et al 2017), and lowering of cholesterol is a major target of risk reduction programmes and guidelines, including the European Task Force, which consists of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (Catapano et al 2016). A 10% reduction in total cholesterol levels in middle-aged men, for example, results in a 50% reduction in heart disease rates within 5 years (Timmis et al 2017). Evidence from multiple meta-analyses and individual randomised clinical trials show a consistent and graded reduction in ASCVD risk in response to reductions in total cholesterol and LDL-C levels (Catapano et al 2016). These trials consistently showed that higher initial LDL-C levels resulted in greater absolute reduction in ASCVD risk, while the relative risk reduction remained constant at any given baseline LDL-C level (Catapano et al 2016).

Familial hypercholesterolemia (FH) is an autosomal dominant disorder that is manifested by lifelong and marked elevation in LDL-C and premature ASCVD (Sjouke et al 2011, Alonso-Gonzalez and Dimopoulos 2013). There are at least 20 million people with FH worldwide, but the majority remain undiagnosed (~90%) and current treatment is often suboptimal. If untreated, men with FH have a 50% risk of fatal or nonfatal CHD by 50 years of age, and women have a 30% risk by 60 years of age (Zamora et al 2017). Global Burden of Disease project reports that in 2015 in Europe overall there were 11.3 million new cases of cardiovascular disease (CVD), with just over half of these being ischemic heart disease (Wilkins et al 2017). In Europe in 2017, 45% of deaths from ischemic heart disease and 29% of deaths from CVD were attributed to high LDL-C (Institute for Health Metrics and Evaluation 2019).

Patients with heterozygous FH (HeFH) have LDL-C levels 2-to 3-fold higher than normal (7.8-13.0 mmol/L or 300-500 mg/dL), while patients with homozygous FH (HoFH) have LDL-C levels ranging between 3- to 6-fold higher than normal (13-26 mmol/L or 500-1,000 mg/dL). Given the very high baseline LDL-C, many FH patients (both homozygous and heterozygous) are refractory to drug treatment and require more aggressive measures, including apheresis, ileal bypass surgery, portocaval anastomosis, and liver transplantation (Thompson 2008). In addition, levels of proprotein convertase subtilisin kexin 9 (PCSK9; a member of the serine protease family) have been shown to be significantly elevated in both untreated HeFH and

HoFH patients compared with untreated controls. Interestingly, these high baseline PCSK9 levels increase further (by 20%-35%) with statin treatment (Raal et al 2013). Thus, there are a large number of patients with HeFH and HoFH with a high-unmet need for therapies that can lower their PCSK9 levels and allow them to achieve their LDL-C goals.

2.1 Indication

Inclisiran is indicated in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Incidence:

Incidence data are not provided as incidence is not an appropriate calculation for a chronic condition such as ASCVD.

Prevalence:

Hyperlipidemia is most common in high income countries, and the World Health Organization reports that Europe has the greatest proportion in the Northern Hemisphere with 54% prevalence (Timmis et al 2017). According to the ESC Atlas, the mean age standardised- prevalence of hyperlipidemia (≥6.2 mmol/L) averaged across 56 ESC member countries was 16.4% and 15.8% in women and men, ranging from <10% in Azerbaijan, Bosnia and Herzegovina, Republic of Georgia, Kyrgyzstan, Republic of Moldova, and Turkey to >20% in Belgium, Finland, France, Germany, Ireland, Norway, and the United Kingdom (Timmis et al 2017). Within the EU, for both sexes combined, the prevalence of blood cholesterol >6.2mmol/L ranged from 12.1% in Romania to 25.6% in Luxembourg. Outside of the EU, the prevalence of blood cholesterol >6.2mmol/L varied from 4.6% in Tajikistan to 29.1% in Iceland (Wilkins et al 2017).

Recent data suggest that the prevalence of FH may be as high as 0.4%, worldwide (Pérez de Isla et al 2017). The prevalence of HoFH is one in a million compared with 1 in 200 to 500 for HeFH, except in regions with high consanguinity rates, such as South Africa, Lebanon, and Quebec, where prevalence of HeFH is close to 1 in 100 (Zamora et al 2017, O'Brien et al 2014, Nordestgaard et al 2013).

The prevalence of elevated total cholesterol above 5 mmol/L (200 mg/dL) was 38% in outpatients studied in a global registry, with a higher percentage observed in Eastern European countries (Bulgaria, Lithuania, Romania, Ukraine, Hungary, and Russia) (Venkitachalam et al 2012).

Data for 2009 from the ESC Atlas showed that the mean blood cholesterol concentration averaged across all ESC member countries was 5.1 mmol/L in both women and men, ranging from 4.5 and 4.4 mmol/L in women and men from Kyrgyzstan to 5.6 mmol/L in women and men from Iceland (Timmis et al 2017).

Demographics of the population in the proposed indication and risk factors for the disease:

Few published studies reported on demographic distribution of patients with hyperlipidemia in Europe.

In a cross-sectional study of 14,699 patients with FH from the Catalonia, Spain, Information System for the Development of Research in Primary Care, there was a higher rate of FH in men between the ages of 25 to 54, and a higher rate in women 55 years of age and older (Zamora et al 2017). In this study, patients with FH were older when compared with the general population of 2,539,944 patients (mean age: 61.5 vs 54.1 years, respectively) and had a higher prevalence of cardiovascular risk factors (diabetes mellitus, hypertension, renal function, smoking, obesity). Within the population that was 35 to 59 years of age (mean age: 50.3 years), the prevalence of CHD was 4.75 times higher in patients with FH compared with the general population. In the 36 to 45 years of age group, CHD prevalence was 8.2 and 6.4 times higher in women and men, respectively, than in the general population (Zamora et al 2017).

As stated previously, FH prevalence is higher in some populations such as Afrikaners, French Canadians (Quebecois), Finnish, and Lebanese, where there are founder effects and relatively isolated populations (Zamora et al 2017, Hovingh et al 2013). The highest prevalence of FH is seen in the Afrikaner population (HeFH is estimated as 1 in 70). In French Canadians, 1 in 270 is estimated to have HeFH. There is a wide distribution and range of FH mutations in European populations, with some showing considerable heterogeneity (eg, French and Italian), while others involve a narrow range of causative mutations and are relatively homogeneous (Hovingh et al 2013).

In the EUROASPIRE V cross-sectional survey of hospitalised patients with CHD, full results were available from 7824 patients at 130 centres in 27 countries (De Backer et al 2019). Patients were, on average, 63.6 years of age (standard deviation: 9.6 years) and 25.7% were females.

De Backer et al, showed lipid profiles across the participating countries in EUROASPIRE V and illustrate the large heterogeneity between countries in the proportions with elevated TC, LDL-C, and non-high-density lipoprotein cholesterol (De Backer et al 2019). There were also considerable differences in the lipid profile between patients from different centres within a given country.

Risk factors

Risk factors for the development of ASCVD include secondary hyperlipidemias, in addition to genetic disorders such as FH (Ibrahim et al 2019, Catapano et al 2016, Stone et al 2014) Examples of such risk factors are as follows:

- Positive family history of premature ASCVD (males younger than 55 years and females younger than 65 years)
- Age (male 45 years or older, female 55 years or older)
- Smoking
- Obesity
- Diet (trans fats, saturated fat, sugar, and [to a lesser extent] cholesterol in the food raise total and LDL-C levels)

- Level of physical activity (increased physical activity helps to lower LDL-C and raise high-density lipoprotein cholesterol level)
- Metabolic syndrome (hypertension, diabetes mellitus, abdominal obesity)
- Co-morbidities (hypothyroidism, cholestasis, nephrotic syndrome, chronic renal failure, lipodystrophies)
- Certain drugs (thiazide diuretics, amiodarone, beta blockers [not carvedilol], bile acid sequestrants, glucocorticoids, cyclosporine, sirolimus, oral estrogens, raloxifene, tamoxifen, anabolic steroids, protease inhibitors, retinoic acid).

The main existing treatment options:

The targeted approach to lipid management for the prevention of ASCVD is primarily aimed at reducing LDL-C. Achieving an LDL-C level of <1.8 mmol/L (70 mg/dL) is recommended, or a reduction of at least 50% if the baseline LDL-C level is between 1.8 and 3.5 mmol/L (70–135 mg/dL) (De Backer et al 2019, Catapano et al 2016). Treatments for hyperlipidemia consist of medications to lower LDL-C, including the following (Catapano et al 2016):

- Statins
- The cholesterol absorption inhibitor, ezetimibe
- PCSK9 monoclonal antibodies (ie, evolocumab or alirocumab)
- Niacin and fibrates
- Bile acid sequestrants (ie, cholestyramine, colestipol, colestid, and colesevelam)
- Drug combinations (eg, statins and ezetimibe, statins and bile acid sequestrants)

Lifestyle modifications are also indicated, including cessation of smoking, regular physical exercise at moderate to vigorous intensity, weight control, and a healthy diet to avoid weight gain or, in overweight and obese patients, to promote weight loss.

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

Left untreated, hyperlipidemia is a causal factor of ASCVD, the consequences of which are high numbers of disability-adjusted life years, heart attack, stroke or other occlusive arterial disease, and sudden cardiac death (De Backer et al 2019, Catapano et al 2016). The risk of ASCVD death increases linearly with increasing blood cholesterol levels. If untreated, men and women with HeFH with total cholesterol levels of 8-15 mmol/L (310-580 mg/dL) typically develop ASCVD before age 55 and 60, respectively, while men and women with HoFH and total cholesterol levels of 12–30 mmol/L (460-1160 mg/dL) typically develop ASCVD very early in life, and if untreated die before age 20 (Nordestgaard et al 2013).

The latest available data show that ASCVD accounted for over 3.8 million deaths each year, or 45% of all deaths across ESC member countries (Timmis et al 2017).

Premature deaths are of interest since many are deemed to be preventable through reduced exposure to behavioural risk factors plus timely and effective treatment. According to the ESC Atlas, although around 65% of all ASCVD deaths in the member countries of the ESC occurred in individuals over 75 years of age, approximately 1.3 million people under 75 and approximately 635000 under 65 died each year from ASCVD. This makes ASCVD the leading

cause of premature death, responsible for 35% of deaths in people under 75 years of age and 29% of deaths in those under 65 years of age, compared with 29% (1.1 million) and 27% (607,000) deaths, respectively, from cancer (Timmis et al 2017).

The potential years of life lost (PYLL) provides another measure of premature mortality and is calculated by summing up deaths occurring at each age and multiplying this by the number of remaining years to live up to a selected age limit (75 years for the data presented here). In this way, PYLL adds greater weight to the deaths occurring at younger rages. ASCVD makes a considerable yet variable contribution to PYLL in the member countries of the ESC. Among men, data from 2007-2014 showed that ASCVD accounted for between 11% of PYLL in France and 39% of PYLL in Bulgaria. Among women, the contribution ranged from 7% in Iceland, Israel and Luxembourg to 33% in Bulgaria. The contribution of ASCVD to PYLL is lower in high income than middle income countries both for women (13% vs. 23%) and for men (20% vs. 27%) (Timmis et al 2017). In Europe as a whole, high LDL-C was responsible for 11% of all PYLL in 2017 (Institute for Health Metrics and Evaluation 2019).

Important co-morbidities:

Co-morbidities that, in addition to hypercholesterolemia, contribute to the development of ASCVD include diabetes mellitus (type 2 and type 1 of more than 15 years duration or with 2 or more major cardiovascular risk factors such as albuminuria, chronic kidney disease, initiation of intensive control >5 years after diagnosis, poorly controlled haemoglobin A1C, or insulin resistance with metabolic syndrome) hypertension, obesity, hypothyroidism, cholestasis, nephrotic syndrome, chronic renal failure, and lipodystrophies (Timmis et al 2017, Jellinger et al 2017).

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

The pharmacology, safety pharmacology, drug metabolism, pharmacokinetic, and toxicology of inclisiran were evaluated in a series of in vitro and in vivo nonclinical studies. Nonclinical toxicology studies in rats (up to 29 weeks duration) and cynomolgus monkeys (up to 40 weeks duration) showed that inclisiran was well tolerated, did not demonstrate dose limiting toxicities and provided large safety margins for the dose range and schedule planned for inclisiran administration in humans. Inclisiran had no effect on the respiratory, central nervous or cardiovascular systems. Preclinical data suggest an absence of drug-drug interactions with inclisiran. Inclisiran is not genotoxic and does not have carcinogenic potential. Inclisiran did not show any signs of developmental or reproductive toxicity, however no data are available on the use of inclisiran in pregnancy. Based on the comprehensive testing performed, no additional nonclinical studies are warranted [2.4 Nonclinical Overview].

Results of the nonclinical studies do not raise concerns in relation to human safety.

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
<u>Reproductive toxicity studies</u> Inclisiran did not show positive signals for selective reproductive toxicity in fertility and early embryonic development studies conducted in rats, embryo-foetal development studies conducted in rats and rabbits, and a pre and postnatal development study conducted in rats. There was no effect of inclisiran on paternal performance, spermatogenesis, oestrous cycle, and uterine or ovarian parameters and inclisiran did not show evidence of embryo lethality, fetotoxicity, or teratogenicity. In addition, there were no effects of inclisiran on the development of the F_1 generation, including survival, growth, physical and reflexological development, behaviour, and reproductive performance.	There was no evidence of reproductive toxicity in animal models. As pregnant women were excluded from clinical trials, there are no data from the use of inclisiran in pregnant women. Therefore, as a precautionary measure, it is preferable to avoid the use of inclisiran during pregnancy.
<u>Genotoxicity studies</u> Inclisiran was tested in a series of in vitro and in vivo genetic toxicology studies, including a bacterial mutagenicity assay, an in vitro chromosome aberration assay using human peripheral lymphocytes, and an in vivo bone marrow micronucleus assays in rats. There were no gene mutations or chromosomal damage observed in any study. Therefore, inclisiran is not genotoxic.	Inclisiran is not genotoxic. No genetoxicity effects are anticipated in humans with inclisiran use.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Carcinogenicity study	
Inclisiran was not carcinogenic in Sprague-Dawley rats or in TgRasH2 mice administered inclisiran at doses sufficiently in excess of clinical doses.	Based on the results of carcinogenicity studies no carcinogenic effects are expected with inclisiran usage.
Local Tolerance	
Dedicated local tolerance studies with inclisiran have not been conducted; however, extensive injection site analysis was incorporated into all pivotal toxicology studies. In general, inclisiran was well tolerated at the injection sites. There were sporadic instances of local erythema and edema associated with discolouration that were slight to moderate in severity, not associated with microscopic findings, self-limiting, and not present following recovery periods.	The risk of local reactions at the injection site is relevant to human usage. In clinical trials, adverse events (AEs) at the injection site occurred more frequently with inclisiran than placebo. However, AEs at the injection site were localised, predominantly mild or occasionally moderate, transient, and resolved without sequelae.

Source: [2.6.4 Pharmacokinetics Written Summary], [2.6.6 Toxicology Written Summary], [2.5 Clinical Overview]

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

Clinical development programme:

The clinical development program consists of 7 Phase I and Phase II supportive studies in a total of 681 subjects and 3 adequate and well controlled confirmatory Phase III studies in a total of 3,660 subjects. These 3 confirmatory studies were near-identical in design, with 18 months treatment observation to enable data pooling where appropriate.

In addition, three cardiovascular outcomes studies have planned enrollment of more than 47,000 subjects, with more than 34,000 subjects already been randomized. Phase II and a Phase III long term extension studies are completed.

The goal of the inclisiran clinical development programme was to demonstrate inclisiran's ability to significantly lower PCSK9 and LDL-C and to reduce the risk of Major Adverse Cardiovascular Events (MACE) defined as a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke and urgent coronary revascularization while maintaining an acceptable safety profile.

Pooled data from the Phase III placebo-controlled studies (i.e., Controlled Phase III Safety Pool) were used to calculate the cumulative clinical trial exposure [2.7.4 Summary of Clinical Safety].

Table 4-1 SIII.1 Duration of exposure based on pooled data from Phase III studies (ORION-9, 10, and 11)

Number of study doses administered	Inclisiran (N=1833)	Person Years
1	41	33.38
2	64	66.69
3	62	81.91
4	1666	2455.51
Total	1833	2637.48

Table 4-2 SIII.2-Exposure by age group and gender based on pooled data from Phase III studies (ORION-9, 10, and 11)

Age group	Patients		Person Years	
	Male (N=1228)	Female (N=605)	Male	Female
<18 years	0	0	0.00	0.00
18 to <60 years	100	49	145.91	70.61
60 to <65 years	481	222	697.62	317.17
65 to <75 years	481	261	692.63	371.40
≥ 75 years	166	73	235.07	107.07
18 to <65 years	581	271	843.53	387.78
≥65 years	647	334	927.70	478.47
Total	1228	605	1771.23	866.25

Table 4-3 SIII.3-Exposure dose based on pooled data from Phase III studies (ORION-9, 10, and 11)

Dose of exposure	Patients	Person Years
300 mg	1833	2637.48

Table 4-4 SIII.4-Exposure by race based on pooled data from Phase III studies (ORION-9, 10, and 11)

Ethnic origin	Inclisiran (N=1833)	Person Years
American Indian or Alaska Native	4	5.99
Asian	22	32.53
Black or African American	131	182.31
Native Hawaiian or other Pacific Islander	7	9.58
White	1669	2407.06
Total	1833	2637.48

Table 4-5 SIII.5-Exposure by ethnic origin based on pooled data from Phase III studies (ORION-9, 10, and 11)

Ethnic origin	Inclisiran (N=1833)	Person Years
Hispanic or Latino	120	167.54
Not Hispanic or Latino	1713	2469.94
Total	1833	2637.48

Data from Study CKJX839A12201E1 (ORION-3; Phase II open-label, active comparator extension study) were used to calculate the long-term exposure to study treatment. The median duration (min, max) of exposure in ORION-3 to study treatment for the inclisiran only arm safety population was 1443 (71, 1610) days, and the total exposure in ORION-3 was 1045.5 person years. ORION-3 was an extension study of ORION-1. The median duration (min, max) of exposure from ORION-1 through ORION-3 for ORION-3 inclisiran only arm safety population was 1654 (281, 1820) days, and the total exposure from ORION-1 through ORION-3 was 1209.6 person years [CKJX839A12201E1].

Data from Study CKJX839A12306B (ORION-8; Phase III open-label, long-term extension study) were used to calculate the long-term exposure to study treatment. For the 3274 subjects in ORION-8 safety population, the median duration (min, max) of exposure to inclisiran in ORION-8 was 1081.0 (2, 1228) days, and the total exposure in ORION-8 was 8529.87 person years [CKJX839A12306B (ORION-8)] CSR. ORION-8 is an extension study of ORION-3, ORION-9, ORION-10 and ORION-11. For the 3712 subjects who have received at least one dose of inclisiran sodium 300 mg in ORION-1 (parent study of ORION-3), ORION-3, ORION-9, ORION-10, ORION-11, or ORION-8, the median duration (min, max) of exposure to inclisiran in those studies combined was 3.070 (0.005, 6.839) years, and the total exposure to inclisiran in those studies was 12802.5 person years [CKJX839A12306B (ORION-8) SCS].

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
New York Heart Association class IV heart failure or last known left ventricular ejection fraction <25%	Severity of this co-morbidity makes a subject unsuitable for a Phase III placebo-controlled study as the condition would require active clinical management.	No	Use of inclisiran in this population is not anticipated to be associated with any additional risks.
Cardiac arrhythmia within 3 months prior to randomisation that was not controlled by medication or via ablation	Severity of this co-morbidity makes a subject unsuitable for a Phase III placebo-controlled study as the condition require clinical management.	No	Use of inclisiran in this population is not anticipated to be associated with any additional risks.
Major adverse cardiovascular event within 3 months prior to randomisation	Severity of this recent significant co-morbidity makes a subject unsuitable for a placebo-controlled Phase III study.	No	Use of inclisiran in this population is not anticipated to be associated with any additional risks. Lowering of LDL-C is considered a foundation of medical management to prevent recurrence of such events.
Uncontrolled severe hypertension: SBP >180 mmHg or DBP >110 mmHg prior to randomisation despite anti-hypertensive therapy	Severity of this co-morbidity and need for clinical management makes a subject unsuitable for a Phase III study as additional measures to control BP could jeopardize the conduct of the study.	No	Use of inclisiran in this population is not anticipated to be associated with any additional risks. On the contrary, this would be considered as appropriate multiple risk factor management.
Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology	Pre-existing liver dysfunction makes a subject unsuitable for this Phase III due to the limited amount of data available at the time the	No	The ORION-6 study concluded that no dose adjustments are necessary for patients with mild to moderate hepatic impairment.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
of the liver or unexplained elevations in ALT, AST, >3x the ULN, or total bilirubin >2x ULN at screening confirmed by a repeat abnormal measurement at least 1 week apart.	Phase III started to ensure safety in this population.		The data from the Phase III studies shows no clinically relevant adverse effect in liver function in patients exposed up to 18 months.
Treatment (within 90 days of screening) with monoclonal antibodies (mAb) directed towards PCSK9	Concomitant use would confound interpretation of the efficacy results.	No	In order to properly assess efficacy, a true LDL-C baseline is required. As washout of a mAb to PCSK9 takes approximately 90 days, a mAb received within 90 days would impact efficacy results. Inclisiran is not intended for concomitant use with monoclonal antibodies directed towards PCSK9.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase AST=aspartate aminotransferase; BP=blood pressure; CV=cardiovascular; DBP=diastolic blood pressure; mAb=monoclonal antibody; PCSK9= proprotein convertase subtilisin/kexin type 9; SAE=serious adverse event; SBP= systolic blood pressure; ULN=upper limit of normal

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect rare or very rare adverse reactions (occurring less than 0.1%).

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 SIV.2-Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breast-feeding women	
Patients with relevant co-morbidities:	
Patients with renal impairment	The following data are included for patients with renal impairment (estimated glomerular filtration rate [eGFR])

Type of special population	Exposure
	End Stage Renal Disease (<15 mL/min/1.73 m^2): no patients included in the clinical development programme Severe (≥15 to <30 mL/min/1.73 m^2): 4 persons (4.76 person years) Moderate (≥30 to <60 mL/min/1.73 m^2): 195 persons (277.92 person years) Mild (≥60 to <90 mL/min/1.73 m^2): 639 persons (918.58 person years) Normal (≥90 mL/min/1.73 m^2): 995 persons (1436.22 person years)
Patients with hepatic impairment	Severe (Child Pugh Class C): no patients included in the clinical development programme Moderate (Child Pugh Class B): 6 persons (2.87 person years) Mild (Child Pugh Class A): 10 persons (4.99 person years)
Patients with cardiovascular impairment	ASCVD: 1553 persons (2229.49 person years) ASCVD risk equivalent: 280 persons (407.99 person years)
Immunocompromised patients	Immunosuppression was not assessed in clinical trials and was not a criteria for inclusion/exclusion; therefore, unable to quantify exposure. However, the use of inclisiran in this population, where indicated, is likely to be safe and effective.

ASCVD=atherosclerotic cardiovascular disease

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated on worldwide sales volume in person years based on the number of inclisiran pre-filled syringes sold. Pre-filled syringes are designed for single use and hence it is assumed that each pre-filled syringe represents one injection to one patient. Each pre-filled syringe contains 1.5 mL of solution containing 284 mg inclisiran.

Based on World Health Organization (WHO) guidance, the recommended maintenance dose (long-term therapeutic dose) is preferred when establishing the defined daily dose (DDD). The initial dose may differ from the maintenance dose, but this is not reflected in the DDD.

Considering the recommended dose of inclisiran is 284 mg administered as a single subcutaneous injection: initially, again at three months, and followed by every six months, each patient may use two pre-filled syringes per year. Therefore, two pre-filled syringes per patient per year is used as a basis for the estimate of the person years exposure to inclisiran.

6.1.2 Part II Module SV.1.2. Exposure

Table 6-1 Cumulative exposure from marketing experience

	EEA	USA and Canada	ROW	Total
Number of pre-filled syringes	CCI [redacted]	[redacted]	[redacted]	[redacted]
Patient Treatment years	25,488	24,666	21,842	**71,996**

EEA: European Economic Area; IBD: International Birth Date; ROW: Rest of the World.
This table includes cumulative data obtained from IBD (09 Dec 2020) to 30 Jun 2023.
Note: Sales from the United Kingdom are considered under ROW.
Source of data: worldwide sales volume.

The patient exposure based on demographics (i.e. sex, age) could not be estimated as the data based on demographics was not available.

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

Inclisiran is not chemically or pharmacologically similar to other drugs with known abuse potential. In addition, no psychoactive effects have been observed in clinical studies that would suggest potential abuse with inclisiran. Psychoactive effects and dependence are not expected in this class of drugs as they are not active in the central nervous system. Inclisiran will be administered by a health care professional, further limiting any potential for misuse. Therefore, no formal clinical or nonclinical studies have been conducted to assess the possibility that inclisiran may be misused or abused.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

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

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

Table 8-1 Risks not considered important for inclusion in the list of safety concerns

Risk	Reason for not including as a safety concern in the RMP
Adverse events at the injection site	Known risks that do not impact the risk-benefit profile. Adverse events at the injection site were the only adverse drug reactions identified in the clinical development program. AEs at the injection site occurred more frequently with inclisiran than placebo in the Phase III confirmatory studies. However, AEs at the injection site were localised, predominantly mild or occasionally moderate, transient, and resolved without sequelae. In addition, administration of inclisiran does not lead to any long-term changes in any tissues local to the injection site. Therefore, as all medicines given as a subcutaneous injection have the potential and likelihood to cause local reactions at the site of injection, these adverse drug reactions are not qualified as an important risk for inclusion in the list of safety concerns.
Hepatotoxicity	No concerns related to hepatic safety emerged from the assessments in the ORION clinical development program. Therefore, inclusion of hepatotoxicity in the RMP as an important potential risk is not warranted. The non-clinical program did not identify an adverse effect of inclisiran on hepatic function. No difference in safety profile has been demonstrated in the hepatic impairment study (ORION-6) comparing the subjects with normal, mild and moderate impairment in liver function. Substantial data to assess hepatic safety were collected in the placebo-controlled phase III studies, with a long-term treatment period of 18 months with a cumulative clinical trial exposure of 2652.6 person-years for inclisiran. Analysis of pooled safety data from phase III clinical studies showed: • No imbalance between the placebo-treated and inclisiran-treated subjects in the frequency of treatment emergent adverse events (TEAEs) related to hepatic safety. TEAES were identified by the predefined SMQ search [SCS section 2.1.4.2.3]. • No difference between the placebo and inclisiran treatment groups in the incidence of clinically significant (CS) elevations of transaminases (elevations above 3 x ULN) and other biomarkers of hepatic safety (total bilirubin and ALP). There were no cases meeting the definition of Hy's Law.

Risk	Reason for not including as a safety concern in the RMP
	Very few hepatic related treatment emergent AEs and clinically significant elevations in ALT/AST were observed in long-term open-label extension studies for up to 34 months of inclisiran treatment. Based on totality of the data, inclisiran is not associated with hepatotoxicity. Therefore, Novartis does not consider hepatotoxicity as a safety concern for inclisiran. Hepatotoxicity will continue to be monitored in clinical trials and through routine pharmacovigilance post-approval and will be presented in the PSUR as a safety topic.
Off-target effects in patients with severe renal impairment	Nonclinical data do not indicate a potential for increased risk in the renally impaired patient population. Based on the totality of data from clinical trials, there is no evidence of a relationship between degree of renal impairment and changes in safety profile of inclisiran, including renal function. However, based on the limited safety data in patients with severe renal impairment, a statement is included in the SmPC Section 4.2, that inclisiran should be used with caution in these patients. Since no safety concern has become evident so far in these patients, 'off-target effects in patients with severe renal impairment' is not included in the list of safety concerns in the RMP. Use in patients with severe renal impairment will be further evaluated in the PSURs.

8.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risks

There are no important identified risks.

Important potential risks

There are no important potential risks.

Missing information

Table 8-2 Missing information

Missing information	Risk-benefit impact (Reasons for classification as missing information)
Long-term safety	The current data do not suggest an adverse effect of long-term exposure to inclisiran up to 18 months in the Phase III trials and up to 48 months in the ongoing extension trials. The long-term safety of inclisiran is currently under evaluation in the two ongoing studies ORION-3, and ORION-8. Since these studies may provide relevant information regarding the long-term safety of inclisiran, long-term safety is considered as missing information in the RMP.
Use in pregnancy and breast-feeding	In the inclisiran clinical development program, two inclisiran exposed pregnancies have occurred. PD [redacted] There are limited clinical data from the use of inclisiran in pregnant women.

Missing information	Risk-benefit impact (Reasons for classification as missing information)
	Inclisiran has not been evaluated during either pregnant women or nursing mothers. Although inclisiran was observed in the milk of lactating rats, there is no evidence of systemic absorption in the suckling rat neonates and no adverse effects on offspring were observed.
Use in patients with severe hepatic impairment	There is no evidence of liver toxicity from the completed comprehensive nonclinical and clinical programs conducted with inclisiran. Patients with severe hepatic impairment were excluded from the development program, including the pivotal Phase III clinical studies. A specific Phase I study [ORION-6] in subjects with normal, mild or moderate hepatic impairment was conducted and inclisiran was safe and well-tolerated in all subjects regardless of hepatic function status [Module 2.5 Clinical Overview Section 3.3.2].

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

As per the PRAC recommendation, the missing information "Long-term safety" is removed from the list of safety concerns considering that the ORION-8 study is complete and long-term safety data from the ORION-8 study covered the knowledge gap of long-term safety for inclisiran. The safety data reported from this long-term extension study ORION-8 do not change the safety profile of inclisiran. No new safety concerns were identified based on ORION-8 study. Additionally, there are neither further aPhV activities or aRMMs in place for long-term safety, nor introduction of new aPhV activities for long-term safety are necessary.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable as there are no important identified and important potential risks.

8.3.2 Part II Module SVII.3.2. Presentation of the missing information

Table 8-3 Missing information: Use in pregnancy and breast-feeding

Use in pregnancy and breast-feeding	Details
Evidence source	Anticipated risk/consequence of the missing information: Inclisiran has not been evaluated in pregnant and breast feeding women. There are limited clinical data from the use of inclisiran in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Although inclisiran was observed in the milk of lactating rats, there is no evidence of systemic absorption in suckling rat neonates and no adverse effects on offspring were observed.

Table 8-4 Missing information: Use in patients with severe hepatic impairment

Use in patients with severe hepatic impairment	Details
Evidence source	Anticipated risk/consequence of the missing information: Patients with severe hepatic impairment (Child Pugh Class C) were not included in the clinical development program. In the real-world setting, very few patients with severe hepatic impairment are expected to receive inclisiran. No safety concerns of clinical significance are anticipated if inclisiran is administered to patients with severe liver disease based on the available data from patients with mild to moderate hepatic impairment. Therefore, the medical decision should be made by the prescriber based on clinical judgement and expected benefit-risk for the patient. Of note, a precaution for use in patients with severe hepatic impairment is stated in the SmPC Section 4.2.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Part II SVIII.1: Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy and breast-feeding Use in patients with severe hepatic impairment

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

The pharmacovigilance plan does not include any routine pharmacovigilance activities beyond signal detection and reporting of adverse reactions.

10.2 Part III.2. Additional pharmacovigilance activities

CKJX839A12011, Inclisiran PRegnancy outcomes Intensive Monitoring (PRIM) is an ongoing study to monitor and further characterize the missing information of 'use in pregnancy and breast-feeding'.

10.2.1 Inclisiran PRegnancy outcomes Intensive Monitoring (PRIM)

Study short name and title:

CKJX839A12011: Monitoring of pregnancy outcomes in women treated with inclisiran: a non-interventional study

Rationale and study objectives:

PRIM as an additional pharmacovigilance activity is intended to monitor actual use in pregnancy and to proactively collect pregnancy outcomes for reported cases.

The overall objective of the inclisiran PRIM program is to collect data on pregnancy outcomes in patients treated with inclisiran during pregnancy or prior to pregnancy (including congenital malformations, spontaneous abortions, stillbirths and other adverse birth outcomes) as well as infant outcomes at 3 and 12 months post-delivery, including breast-feeding status and exposures, neonatal and infant deaths, neonatal and infant hospitalizations and developmental delays. The findings from this program will be used to evaluate the missing information 'Use in pregnancy and breast-feeding', according to the RMP.

Study design:

The PRIM is a non-interventional post-authorisation safety study (PASS) utilizing a structured approach for data collection with targeted questionnaires to obtain follow-up information from exposed pregnancies with improved collection, quality, and processing of information.

Study population:

All prospective and retrospective pregnancy cases exposed to inclisiran during pregnancy or prior to LMP reported to Novartis safety database (Argus) will be eligible for PRIM study. This includes cases from spontaneous post-marketing report sources, Novartis clinical trials, post-marketing observational studies, patient-oriented programs (if applicable), and scientific publications.

Milestones:

Interim progress report: Annual interim progress reports will be provided with PSURs

Final report: 31-Jul-2031.

The PRIM NIS will apply until a maximum of 10 years from the first launch or 500 prospectively reported live births with known status of malformations, whichever occurs first.

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Inclisiran PRegnancy outcomes Intensive Monitoring (PRIM) Status: Ongoing	The overall objective of the inclisiran PRIM program is to collect data on pregnancy outcomes in patients treated with inclisiran during pregnancy or prior to pregnancy (including congenital malformations, spontaneous abortions, stillbirths and other adverse birth outcomes) as well as infant outcomes at 3 and 12 months post-delivery, including breast-feeding status and exposures, neonatal and infant deaths and developmental delays. The findings from this program will be used to evaluate the missing information 'Use in pregnancy and breast-feeding', according to the RMP.	Use in pregnancy and breast-feeding	Interim progress reports: Final report submission	Annual interim progress reports will be provided with PSURs. 31-Jul-2031 The PRIM NIS will apply until a maximum of 10 years from the first launch or 500 prospectively reported live births with known status of malformations, whichever occurs first.

11 Part IV: Plans for post-authorization efficacy studies

Not applicable

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Use in pregnancy and breast-feeding	**Routine risk minimization measures:** SmPC Section: 4.6 PL Section: 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.6 recommends that as a precautionary measure, it is preferable to avoid the use of inclisiran during pregnancy. Section 4.6 also recommends that a decision must be made whether to discontinue breast feeding or to discontinue/abstain from inclisiran therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to medical prescription.
Use in patients with severe hepatic impairment	**Routine risk minimization measures:** SmPC Section: 4.2, 5.2 PL Section: 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 recommends that inclisiran should be used with caution in patients with severe hepatic impairment. **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to medical prescription.

12.2 Part V.2. Additional Risk minimization measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

12.3 Part V.3 Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Use in pregnancy and breast-feeding	**Routine risk minimization measures:** SmPC section 4.6 PL section: 2 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PRIM study (Date of final CSR (planned): 31-Jul-2031) The PRIM NIS will apply until a maximum of 10 years from the first launch or 500 prospectively reported live births with known status of malformations, whichever occurs first.
Use in patients with severe hepatic impairment	**Routine risk minimization measures:** SmPC section 4.2, 5.2 PL section: 2 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

13 Part VI: Summary of the risk management plan for Leqvio (inclisiran)

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

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

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

Important new concerns or changes to the current ones will be included in updates of Leqvio's RMP.

13.1 Part VI: I. The medicine and what it is used for

Leqvio is authorised for adults as an adjunct to diet and maximally tolerated statin therapy, for the treatment of primary hypercholesterolemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C) (see SmPC for the full indication). It contains inclisiran as the active substance and it is administered as a subcutaneous injection.

Further information about the evaluation of Leqvio's benefits can be found in Leqvio'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/leqvio

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Leqvio together with measures to minimize such risks and the proposed studies for learning more about Leqvio's risks, are outlined below.

Measures to minimize 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 minimize its risks.

Together, these measures constitute routine risk minimization measures.

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 Leqvio is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI – II.A: List of important risks and missing information

Important risks are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. 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 Leqvio. 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).

Table 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy and breast-feeding Use in patients with severe hepatic impairment

13.2.2 Part VI - II B: Summary of important risks

Table 13-2 Missing information: Use in pregnancy and breast-feeding

Risk minimization measures	**Routine risk minimization measures:** SmPC Section: 4.6 PL Section: 2 **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Inclisiran PRegnancy outcomes Intensive Monitoring (PRIM) See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-3 Missing information: Use in patients with severe hepatic impairment

Risk minimization measures	**Routine risk minimization measures:** SmPC Section: 4.2, 5.2 PL Section: 2 **Additional risk minimization measures:** None

13.2.3 Part VI – II C: Post-authorization development plan

13.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Leqvio.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

Table 13-4 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
CKJX839A12011 Inclisiran PRegnancy outcomes Intensive Monitoring (PRIM)	PRIM as an additional pharmacovigilance activity is intended to monitor actual use in pregnancy and to proactively collect pregnancy outcomes for reported cases. The overall objective of the inclisiran PRIM program is to collect data on pregnancy outcomes in patients treated with inclisiran during pregnancy or prior to pregnancy (including congenital malformations, spontaneous abortions, stillbirths and other adverse birth outcomes) as well as infant outcomes at 3 and 12 months post-delivery, including breast-feeding status and exposures, neonatal and infant deaths, neonatal and infant hospitalizations and developmental delays. The findings from this program will be used to evaluate the missing information 'Use in pregnancy and breast-feeding', according to the RMP.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

None

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Not applicable