

Patient Safety & Pharmacovigilance

European Union Risk Management Plan (EU RMP)

Leqvio™ (Inclisiran) KJX839

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Rationale for submitting an updated RMP: This European Union (EU) Risk Management Plan (RMP) v4.1 is being updated in response to European Medicines Agency (EMA) D120 request for supplementary information received during the review of the type II variation (EMA/VR/0000293324) for the new indications in paediatric patients with heterozygous familial hypercholesterolaemia (HeFH) (aged 12 years and older) and homozygous familial hypercholesterolaemia (HoFH) (aged 12 to less than 18 years).

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v 4.0
Part I	Updated the proposed indication(s) in the European Economic Area (EEA), as per SmPC.
Part II	Module SI: Updated the epidemiology to remove information related to HoFH. Module SIII: Deleted the clinical trial exposure from ORION-13. Module SIV.1: Deleted the exclusion criteria related to ORION-13 study. Module SV.1.2: No updates. Module SVII.2: As per Pharmacovigilance Risk Assessment Committee (PRAC) recommendation, added a statement specifying the rationale for removal of missing information Long term safety from RMP v3.1.
Part III	No changes.
Part IV	No changes.
Part V	No changes.
Part VI	I: Updated with new indication.
Part VII	

Other RMP versions under evaluation

Not applicable

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List of abbreviations

AE	Adverse Event
aPhV	Additional Pharmacovigilance
AR	Assessment Report
aRMM	Additional Risk Minimisation Measures
ASCVD	Atherosclerotic Cardiovascular Disease
CHD	Coronary Heart Disease
CHMP	Committee for Medicinal Products for Human Use
CSR	Clinical Study Report
CVD	Cardiovascular disease
DDD	Defined Daily Dose
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESC	European Society of Cardiology
EU	European Union
HeFH	Heterozygous Familial Hypercholesterolaemia
HoFH	Homozygous Familial Hypercholesterolaemia
IBD	International Birth Date
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
LDL-C	Low-Density Lipoprotein Cholesterol
mAb	Monoclonal Antibodies
MAH	Marketing Authorisation Holder
NIS	Non-Interventional Study
PCSK9	Proprotein Convertase Subtilisin Kexin type 9
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PYLL	Potential Years of Life Lost
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
ROW	Rest of the World
SAE	Serious Adverse Event
SCS	Summary of Clinical Safety
siRNA	Small Interfering Ribonucleic Acid
SOC	System Organ Class
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
TC	Total Cholesterol
TEAE	Treatment Emergent Adverse Event

ULN

Upper Limit of Normal

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 Authorisation Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	LEQVIO™
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Small interfering ribonucleic acid (siRNA)
	Summary of mode of action: Inclisiran is a cholesterol lowering double-stranded 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	[Proposed Summary of Product Characteristics (SmPC)]
Indication(s) in the EEA	Current: Inclisiran is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, 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.

	Proposed: Inclisiran is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet, and in paediatric patients aged 12 years and older with heterozygous familial hypercholesterolaemia (HeFH): • 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.
	Proposed: The recommended dose for adults and paediatric patients aged 12 years and older is 284 mg inclisiran 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.
	Proposed: Not applicable (Paediatric patients aged 12 years and older will use the approved pharmaceutical form.).
Is/will the product be subject to additional monitoring in the EU?	No

2 Part II: Safety specification

2.1 Part II: Module SI: Epidemiology of the indication(s) and target population

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death among adults under 75 years of age in Europe, accounting for over 3.8 million deaths annually ([Halcox et al 2017](#), [McCormack et al 2016](#), [Timmis et al 2017](#), [Catapano et al 2016](#)). It is also a significant contributor to global disability and is projected to remain the top cause of mortality well beyond 2040 ([Foreman et al 2018](#)). The global burden of disease study reported that in 2015, Europe saw 11.3 million new cases of cardiovascular disease (CVD), with more than half classified as coronary heart disease (CHD) ([Wilkins et al 2017](#)). By 2017, 45% of deaths from CHD and 29% of deaths from CVD were attributed to high LDL-C ([Institute for Health Metrics and Evaluation 2019](#)).

While multiple risk factors contribute to ASCVD, evidence from genetic studies, epidemiology, Mendelian randomization analyses, and randomized controlled trials has established elevated LDL-C as a causal and modifiable risk factor, not just a biomarker ([Ference et al 2017](#)).

Given that a substantial portion of CHD cases are linked to hyperlipidaemia ([Timmis et al 2017](#)) lowering cholesterol is a central focus of prevention strategies and clinical guidelines, such as those from the European Task Force, which includes the European Society of Cardiology (ESC) and the European Atherosclerosis Society ([Visseren et al 2021](#)). For example, a 10% reduction in total cholesterol levels among middle-aged men can lower heart disease risk by 50% within five years ([Timmis et al 2017](#)). Meta-analyses and clinical trials consistently show that reductions in total cholesterol and LDL-C lead to decreases in ASCVD risk. The greater the baseline LDL-C, the more substantial the absolute risk reduction, although relative risk reduction remains constant across varying LDL-C levels ([Catapano et al 2016](#)).

Importantly, hyperlipidaemia often begins in childhood or adolescence, particularly in individuals with inherited lipid disorders. Therefore, early diagnosis and prompt initiation of lipid-lowering therapy are critical. The progression and severity of atherosclerosis are closely linked to both the magnitude and duration of elevated LDL-C, as reflected by the cholesterol-year score ([Schmidt et al 1996](#)).

One of the most significant genetic contributors to lifelong hyperlipidaemia is familial hypercholesterolaemia (FH)—an autosomal dominant disorder marked by elevated LDL-C levels from birth and premature ASCVD ([Sjouke et al 2011](#), [Alonso-Gonzalez & Dimopoulos 2013](#)). Despite its prevalence—affecting at least 20 million people worldwide—an estimated 90% of cases remain undiagnosed, and treatment is frequently inadequate. If left untreated, men with FH have a 50% risk of fatal or nonfatal CHD by age 50, and women have a 30% risk by age 60 ([Zamora et al 2017](#)).

Patients with heterozygous FH (HeFH) typically have LDL-C levels 2 to 3 times higher than normal (7.8–13.0 mmol/L or 300–500 mg/dL).

Additionally, levels of PCSK9—an enzyme involved in LDL receptor degradation—are significantly elevated in untreated HeFH patients compared with healthy controls. These levels

rise even further—by 20% to 35%—following statin therapy ([Raal et al 2013](#)). This underscores the continuous need for novel therapies that target PCSK9 and help patients reach their LDL-C goals.

When diagnosed in infancy, HeFH results in coronary events by age 50 in about 50% of men and 25% of women ([Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents 2011](#)).

2.1.1 Indication

Inclisiran is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet, and in paediatric patients aged 12 years and older with HeFH:

- 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

Hyperlipidaemia 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](#)) and 8.9% in children between the ages of 16 and 19 ([Nguyen 2015](#)). According to the ESC Atlas, the mean age standardized- prevalence of hyperlipidaemia (≥ 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 >6.2 mmol/L ranged from 12.1% in Romania to 25.6% in Luxembourg. Outside of the EU, the prevalence of blood cholesterol >6.2 mmol/L varied from 4.6% in Tajikistan to 29.1% in Iceland ([Wilkins et al 2017](#)).

Recent data suggest that the pooled prevalence of FH may be as high as 0.33% for the adult and 0.28% for the paediatric populations, worldwide ([Hu et al 2020](#)). The prevalence of HeFH is 1 in 200 to 500, 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 – age, gender, racial and/or ethnic origin and risk factors for the disease

Few published studies reported on demographic distribution of patients with hyperlipidaemia 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. No sex-related prevalence of FH was observed in children (8-18 years old) ([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. The authors also noted that starting the appropriate treatment before the age of 18 could delay the LDL burden in patients with FH by five years, compared to initiating treatment in older patients ([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 (e.g., 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 7,824 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 total cholesterol (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 hyperlipidaemias, 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 oestrogens, 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.

For **adults**, European guidelines recommend achieving an LDL-C level of <1.8 mmol/L (70 mg/dL) and a LDL-C reduction of at least 50% in individuals at high CV risk, and a target of <1.4 mmol/L (55 mg/dL) and a LDL-C reduction of at least 50% for patients with established ASCVD or individuals at very high CV risk ([Mach et al 2020](#), [Visseren et al 2021](#)). United States (US) guidelines recommend an LDL-C reduction of at least 50% reduction in patients with ASCVD and a LDL-C threshold of 1.8 mmol/L (70 mg/dL) for addition of non-statins to statin therapy in very high risk ASCVD ([Grundy et al 2019](#), [Virani et al 2023](#), [Virani et al 2023](#)).

Non-pharmacological therapy for hyperlipidaemia consists of lifestyle modifications, 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.

Pharmacological treatment for hyperlipidaemia consists of medications to lower LDL-C, including the following:

- Statins
- The cholesterol absorption inhibitor, ezetimibe
- PCSK9 monoclonal antibodies (mAb) (i.e., evolocumab or alirocumab)
- Niacin and fibrates

- Bile acid sequestrants (ie, cholestyramine, colestipol, colestid, and colesevelam)
- The ATP citrate lyase inhibitor bempedoic acid
- Drug combinations (e.g., statins and ezetimibe)

For adolescents with HeFH, a LDL-C target of ≤ 130 mg/dL is generally recommended ([Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents 2011](#)).

Statins are the foundational treatment in adolescents with HeFH ([Wiegman et al 2015](#)). Additional treatment options include ezetimibe, the PCSK9 mAbs, evolocumab and alirocumab as well as LDL-apheresis.

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

If left untreated, hyperlipidaemia 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 ([Nordestgaard et al 2013](#)). Risk stratification studies in young individuals with HeFH are limited, largely because of the long interval between diagnosis and the development of ASCVD. As a result, most of our current understanding is based on data extrapolated from adult studies ([Peterson 2021](#)).

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 635,000 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 ages. 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](#)). After 20 years of statin therapy initiated in childhood, young adults with HeFH showed significantly lower rates of ASCVD-related events (1%) and no deaths (0%) by age 39, compared to their affected parents who began statin treatment later in life, with rates of 26% for ASCVD events and 7% for death at a similar age ([Luirink et al 2019](#)). This landmark cohort study demonstrates that adults with HeFH who began statin therapy in childhood experienced lower rates of ASCVD events compared to their parents with HeFH who initiated treatment in adulthood. Notably, none of the individuals treated since childhood reported significant side effects from long-term statin use.

Important co-morbidities

Co-morbidities that, in addition to hypercholesterolaemia, 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](#)).

2.2 Part II: 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 2-1 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 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.

Key Safety findings (from non-clinical studies)	Relevance to human usage
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 F₁ generation, including survival, growth, physical and reflexological development, behaviour, and reproductive performance.	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 genotoxicity effects are anticipated in humans with inclisiran use.
<u>Carcinogenicity study</u> 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.
<u>Local Tolerance</u> 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 oedema 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]	

2.3 Part II: Module SIII Clinical trial exposure

Clinical development programme in adults

The clinical development programme in adults 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 enrolment 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 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 2-2 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=1,833)	Person Years
1	41	33.38
2	64	66.69
3	62	81.91
4	1,666	2,455.51
Total	1,833	2,637.48

Table 2-3 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=1,228)	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	1,228	605	1,771.23	866.25

Table 2-4 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	1,833	2,637.48

Table 2-5 SIII.4-Exposure by race based on pooled data from Phase III studies (ORION-9, 10, and 11)

Ethnic origin	Inclisiran (N=1,833)	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	1,669	2,407.06
Total	1,833	2,637.48

Table 2-6 SIII.5-Exposure by ethnic origin based on pooled data from Phase III studies (ORION-9, 10, and 11)

Ethnic origin	Inclisiran (N=1,833)	Person Years
Hispanic or Latino	120	167.54
Not Hispanic or Latino	1,713	2,469.94
Total	1,833	2,637.48

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 1,443 (71, 1,610) days, and the total exposure in ORION-3 was 1,045.5 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 1,654 (281, 1,820) days, and the total exposure from ORION-1 through ORION-3 was 1,209.6 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 3,274 subjects in ORION-8 safety population, the median duration (min, max) of exposure to inclisiran in ORION-8 was 1,081.0 (2, 1,228) days, and the total exposure in ORION-8 was 8,529.87 person years [CKJX839A12306B (ORION-8)] CSR. ORION-8 is an extension study of ORION-3, ORION-9, ORION-10 and ORION-11. For the 3,712 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 12,802.5 person years [CKJX839A12306B (ORION-8) SCS].

Clinical development programme in adolescents

The pivotal paediatric programme for inclisiran consists of four studies: two completed studies in adolescents (12 to <18 years) with HeFH (ORION-16) and HoFH (ORION-13), and two similar studies in younger children (age 6 to <12 years with HeFH (ORION-20) and age 2 to <12 years with HoFH (ORION-19)), which are ongoing. These studies are part of the agreed

EMA Paediatric Investigation Plan (PIP) and the US Food and Drug Administration (FDA) Written Request.

ORION-16 had two sequential parts: a 12-month double-blind, parallel group period, in which participants were randomized in a 2:1 ratio to receive either inclisiran sodium 300 mg or placebo (Part 1/Year 1), followed by a 12-month single-arm open-label follow-up period, with all participants receiving inclisiran (Part 2 /Year 2).

During Part 1, participants received inclisiran [inclisiran group] or placebo [placebo group] on Day 1, Day 90 and Day 270. During Part 2, participants randomized to placebo in Part 1 received inclisiran on Day 360, Day 450 and Day 630 [placebo-inclisiran group] and participants randomized to inclisiran in Part 1 received placebo on Day 360 (to maintain the blind) and inclisiran on Day 450 and Day 630 [inclisiran-inclisiran group].

Duration of exposure

In ORION-16, 138/141 (97.9%) participants were administered all 6 doses of study drug, 90/93 (96.8%) participants in the inclisiran-inclisiran group and 48/48 (100%) participants in the placebo-inclisiran group:

- 90 participants in the inclisiran-inclisiran group received all 5 doses of inclisiran and 1 dose of placebo (to maintain the blind).
- 48 participants in the placebo-inclisiran group received 3 doses of placebo and all 3 doses of inclisiran.

Of the remaining 3 participants in the inclisiran/ inclisiran-inclisiran group, 1 participant each received only 1, 2 and 4 doses, respectively, of inclisiran.

The overall patient years of exposure to inclisiran sodium 300 mg was 228.4.

Exposure by age and gender

In ORION-16, all participants were <18 years of age at study entry.

In ORION-16, the distribution by gender was as follows:

- 66/141 (46.8%) participants were male, 42/93 (45.2%) in the inclisiran* group and 24/48 (50%) in the placebo group.
- 75/141 (53.2%) participants were female, 51/93 (54.8%) in the inclisiran* group and 24/48 (50.0%) in the placebo group.

* The 3 participants in the inclisiran/ inclisiran-inclisiran group who received only 1, 2 and 4 doses of inclisiran were female, male and female, respectively.

Exposure by race

In ORION-16, the distribution by race was as follows:

- 128/141 (90.8%) participants were White, 80/93 (86.0%) in the inclisiran* group and 48/48 (100%) in the placebo group.

- 5/141 (3.5%) participants were Black/African American, 5/93 (5.4%) in the inclisiran group and 0/48 (0%) in the placebo group.
- 4/141 (2.8%) participants were Asian, 4/93 (4.3%) in the inclisiran group and 0/48 (0%) in the placebo group.
- 4/141 (2.8%) participants were of other races, 4/93 (4.3%) in the inclisiran group and 0/48 (0%) in the placebo group.

* The 3 participants in the inclisiran/ inclisiran-inclisiran group who received only 1, 2 and 4 doses of inclisiran were all of White race.

Exposure by ethnic origin

In ORION-16, the distribution by ethnic origin was as follows:

- 125/141 (88.7%) participants were Not Hispanic or Latino, 81/93 (87.1%) in the inclisiran* group and 44/48 (91.7%) in the placebo group.
- 13/141 (9.2%) participants were Hispanic or Latino, 11/93 (11.8%) in the inclisiran group and 2/48 (4.2%) in the placebo group.
- For the remaining 3/141 (2.1%) participants (1/93 (1.1%) in the inclisiran group and 2/48 (4.2%) in the placebo group) ethnicity was not reported.

* The 3 participants in the inclisiran/ inclisiran-inclisiran group who received only 1, 2 and 4 doses of inclisiran were all of Not Hispanic or Latino ethnic origin.

2.4 Part II: Module SIV: Populations not studied in clinical trials

2.4.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table 2-7 Important exclusion criteria in pivotal studies in the development programme

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	Severity of this co-morbidity makes a subject unsuitable for a	No	Use of inclisiran in this population is not anticipated to

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
that was not controlled by medication or via ablation	Phase III placebo-controlled study as the condition require clinical management.		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 of the liver or unexplained elevations in ALT, AST, >3x the upper limit of normal (ULN), or total bilirubin >2x ULN at screening confirmed by a repeat abnormal measurement at least 1 week apart.	Pre-existing liver dysfunction makes a subject unsuitable for this Phase III due to the limited amount of data available at the time the Phase III started to ensure safety in this population.	No	The ORION-6 study concluded that no dose adjustments are necessary for patients with mild to moderate hepatic impairment. 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 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.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
			Inclisiran is not intended for concomitant use with mAb 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			

2.4.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programmes

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

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

Table 2-8 SIV.2-Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women Breast-feeding women	Not included in the clinical development programme
Patients with relevant co-morbidities: Patients with renal impairment	The following data are included for patients with renal impairment (estimated glomerular filtration rate) End Stage Renal Disease (<15 mL/min/1.73 m²): no patients included in the clinical development programme Severe (≥15 to <30 mL/min/1.73 m²): 4 persons (4.76 person years) Moderate (≥30 to <60 mL/min/1.73 m²): 195 persons (277.92 person years) Mild (≥60 to <90 mL/min/1.73 m²): 639 persons (918.58 person years) Normal (≥90 mL/min/1.73 m²): 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)

Type of special population	Exposure
	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 criterion 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

2.5 Part II: Module SV: Post-authorisation experience

2.5.1 Part II Module SV.1. Post-authorisation exposure

2.5.1.1 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 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.

2.5.1.2 Part II Module SV.1.2. Exposure

Table 2-9 Cumulative exposure from marketing experience

	EEA			ROW	Total
Number of pre-filled syringes	202,177			279,711	737,164
Patient Treatment years	101,088			139,855	368,582
EEA: European Economic Area; IBD: International Birth Date; ROW: Rest of the World.					

	EEA			ROW	Total
This table includes cumulative data obtained from IBD (09 Dec 2020) to 31 Dec 2024. 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.

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

2.6.1 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.

2.7 Part II: Module SVII: Identified and potential risks

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

2.7.1.1 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 2-10 Risks not considered important for inclusion in the list of safety concerns

Risk	Reason for not being an important risk
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 programme. 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.

Risk	Reason for not being an important risk
Hepatotoxicity	No concerns related to hepatic safety emerged from the assessments in the ORION clinical development programme. Therefore, inclusion of hepatotoxicity in the RMP as an important potential risk is not warranted. The non-clinical programme 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 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. 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.

2.7.1.2 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 2-11 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 programme, two inclisiran exposed pregnancies have occurred. [REDACTED] [REDACTED] There are limited clinical data from the use of inclisiran in pregnant women. 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 programmes conducted with inclisiran. Patients with severe hepatic impairment were excluded from the development programme, 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].

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

There are no new safety concerns or reclassification of safety concerns in this RMP version. Long-term safety, previously classified as missing information, was removed from the list of safety concerns in RMP v3.1 as per the PRAC recommendation in previous procedure (EMA/H/C/005333/II/0021).

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

2.7.3.1 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.

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

Table 2-12 Characterisation of missing information: Use in pregnancy and breast-feeding

Use in pregnancy and breast-feeding	Details
Evidence source	<u>Anticipated risk/consequence of the missing information:</u> 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 2-13 Characterisation of missing information: Use in patients with severe hepatic impairment

Use in patients with severe hepatic impairment	Details
Evidence source	<u>Anticipated risk/consequence of the missing information:</u> Patients with severe hepatic impairment (Child Pugh Class C) were not included in the clinical development programme. 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.

2.8 Part II: Module SVIII: Summary of the safety concerns

Table 2-14 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

3 Part III: Pharmacovigilance plan (including post authorisation safety studies)

3.1 Part III.1. Routine pharmacovigilance activities

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

3.2 Part III.2. Additional pharmacovigilance activities

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

Inclisiran PRenancy 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 programme 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 hospitalisations and developmental delays. The findings from this programme 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 last menstrual period 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 programmes (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 non-interventional study (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.

3.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 3-1 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 authorisation				
None				
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				
None				
Category 3 - Required additional pharmacovigilance activities				
Inclisiran PRenancy outcomes Intensive Monitoring (PRIM) Status: Ongoing	The overall objective of the inclisiran PRIM programme 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 programme will be used to evaluate the missing information 'Use in pregnancy and	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.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	breast-feeding', according to the RMP.			

4 Part IV: Plans for post-authorisation efficacy studies

There are no planned or ongoing post-authorisation efficacy studies.

5 Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

5.1 Part V.1. Routine risk minimisation measures

Table 5-1 Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	None
Important potential risks	None
Missing information	
Use in pregnancy and breast-feeding	Routine risk minimisation measures: SmPC Section: 4.6 PL Section: 2 Routine risk minimisation 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 minimisation measures beyond the Product Information: Legal status: Medicinal product subject to medical prescription.
Use in patients with severe hepatic impairment	Routine risk minimisation measures: SmPC Section: 4.2, 5.2 PL Section: 2 Routine risk minimisation 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 minimisation measures beyond the Product Information: Legal status: Medicinal product subject to medical prescription.

5.2 Part V.2. Additional Risk minimisation measures

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

5.3 Part V.3 Summary of risk minimisation measures

Table 5-2 Summary of pharmacovigilance activities and risk minimisation activities by safety concerns

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in pregnancy and breast-feeding	Routine risk minimisation measures: SmPC section 4.6 PL section: 2 Additional risk minimisation 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 minimisation measures: SmPC section 4.2, 5.2 PL section: 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

6 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 (PL) 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.

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

Leqvio is authorized for adults as an adjunct to diet and maximally tolerated statin therapy, for the treatment of primary hypercholesterolaemia (including heterozygous familial and nonfamilial hypercholesterolaemia), and in paediatric patients aged 12 years and older with heterozygous familial hypercholesterolaemia (HeFH) to reduce 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>

6.2 Part VI: II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Leqvio together with measures to minimise such risks and the proposed studies for learning more about Leqvio's 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 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.

6.2.1 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 minimise 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 6-1 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

6.2.2 Part VI: II B: Summary of important risks

Table 6-2 Missing information: Use in pregnancy and breast-feeding

Risk minimisation measures	Routine risk minimisation measures: SmPC Section: 4.6 PL Section: 2 Additional risk minimisation 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-authorisation development plan.

Table 6-3 Missing information: Use in patients with severe hepatic impairment

Risk minimisation measures	Routine risk minimisation measures: SmPC Section: 4.2, 5.2 PL Section: 2 Additional risk minimisation measures: None
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6.2.3 Part VI: II C: Post-authorisation development plan

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

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

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

Table 6-4 Other studies in the post-authorisation 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 programme 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 hospitalisations and developmental delays. The findings from this programme will be used to evaluate the missing information 'Use in pregnancy and breast-feeding', according to the RMP.

7 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

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

Not applicable.