Summary of risk management plan for PRALUENT (Alirocumab)

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

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

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

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

I. THE MEDICINE AND WHAT IT IS USED FOR

PRALUENT is authorized for indications as noted below. It contains alirocumab as the active substance and it is given subcutaneously.

Primary hypercholesterolemia and mixed dyslipidemia

PRALUENT 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 low density lipoprotein cholesterol (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.

Established atherosclerotic cardiovascular disease

PRALUENT is indicated in adults with established atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

For study results with respect to effects on LDL-C, cardiovascular (CV) events and populations studied see section 5.1.

Further information about the evaluation of PRALUENT's benefits can be found in PRALUENT's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/praluent

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of PRALUENT, together with measures to minimize such risks and the proposed studies for learning more about PRALUENT's risks, are outlined in the next sections.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients;
- Both healthcare professionals and patients are also provided with packaging information relative to the use of medical device, such as Instructions For Use (IFU) and quick reference guide inside the lid packaging; both elements convey key messages for an optimal use of the medical device
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks. Alirocumab is a prescription only medicine.

Together, these measures constitute routine risk minimization measures.

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

As part of routine surveillance, a "specific pregnancy/drug exposure via parent data collection form" is used to document spontaneous or solicited cases of pregnancy exposed to alirocumab.

In addition, a neonates/children form, added to the pregnancy form has been put in place to document any developmental defects up to 6 months post-birth of children whose mothers are exposed to alirocumab during pregnancy.

If important information that may affect the safe use of PRALUENT is not yet available, it is listed under 'missing information' outlined in the next section.

II.A. List of important risks and missing information

Important risks of PRALUENT 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 PRALUENT. 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 (eg, on the long-term use of the medicine);

Table 1: List of important risks and missing information

Important identified risk	Systemic hypersensitivity reactions
Important potential risk	None
Missing information	Use in children and adolescents Use in pregnant and lactating women Use in patients with severe hepatic impairment

II.B. Summary of important risks

Table 2 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any: Important identified risk: Systemic hypersensitivity reactions

Important identified risk: Systemic hypersensitivity reactions	
Evidence for linking the risk to the medicine	Literature, non-clinical, clinical trials
Risk factors and risk groups	No risk groups or risk factors have been identified. Risk factor analyses included: demographics (age, gender, race, ethnicity, BMI) medical history at baseline, estimated glomerular filtration rate, type of hypercholesterolemia and medical history of allergy, region, statin treatment at randomization.
Risk minimization measures	**Routine risk minimization measures:** Labelled in sections 4.4 and 4.8 of the SmPC Labelled in sections 2 and 4 of PL Prescription only medicine
Additional pharmacovigilance activities	None

BMI: Body Mass Index; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 3 - Missing information (Use in children and adolescents) with corresponding risk minimizations activities and additional pharmacovigilance activities if any

Missing information: Use in children and adolescents	
Risk minimization measures	**Routine risk minimization measures:** Labelled in section 4.2 of SmPC Labelled in section 2 of PL Prescription only medicine
Additional pharmacovigilance activities	The PIP includes 3 studies: DFI14223: Pediatric phase 2 dose finding study

Missing information: Use in children and adolescents	
	EFC14643 and EFC14660: pediatric phase 3 study (only EFC14643 is still ongoing)

PIP: Pediatric Investigation Plan; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 4 - Missing information (Use in pregnant and lactating women) with corresponding risk minimizations activities and additional pharmacovigilance activities if any

Missing information: Use in pregnant and lactating women	
Risk minimization measures	**Routine risk minimization measures:** Labelled in section 4.6 of SmPC Labelled in section 2 of PL Prescription only medicine
Additional pharmacovigilance activities	None

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 5 - Missing information (Use in patients with severe hepatic impairment) with corresponding risk minimizations activities and additional pharmacovigilance activities if any

Missing information: Use in patients with severe hepatic impairment	
Risk minimization measures	**Routine risk minimization measures:** Labelled in sections 4.2 and 4.4 of SmPC Labelled in section 2 of PL Prescription only medicine
Additional pharmacovigilance activities	None

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

II.C. Post-authorization development plan

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

Not applicable. There are no studies which are conditions of the marketing authorization or specific obligation of PRALUENT.

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

Table 6: Other studies in post-authorization development plan

ALIROC07997
Purpose of the study:
Monitor muscle events, and liver function and creatine kinase abnormalities in human immunodeficiency virus patients treated with alirocumab by quantifying the incidences of these safety outcomes using existing healthcare databases.

OBS14697

Purpose of the study:

- Evaluate the effectiveness of the PRALUENT dosing recommendations for the 3 dosage regimens approved to date, ie, 75 mg once every two weeks, 150 mg once every two weeks, and 300 mg once every 4 weeks (monthly) to avoid very low LDL-C levels.
- Describe the pattern of PRALUENT utilization in real-world clinical practice with respect to the dosing recommendations in the labelling of the 3 dosage regimens approved to date, ie, 75 mg once every two weeks,150 mg once every two weeks, and 300 mg once every 4 weeks(monthly) to avoid very low LDL-C levels.

EFC14643 (Pediatric Phase 3 study)

Purpose of the study:

- Evaluate the efficacy of alirocumab versus placebo after 24 weeks of double-blind treatment on LDL-C and other lipid parameters, and safety in patients with heterozygous familial hypercholesterolemia 8 to 17 years of age on top of optimal Statin and other lipid modifying therapy.
- Evaluate the efficacy, safety and tolerability of alirocumab after 80 weeks of open-label treatment.

LDL-C: Low Density Lipoprotein Cholesterol.