Summary of the Risk Management Plan (RMP) for Praluent®

Praluent® (alirocumab)
Marketing Autorisation Holder : sanofi-aventis (suisse) sa
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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them. The RMP summary of Praluent® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le medicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Praluent® in Switzerland is the "Arzneimittelinformation/ Information sur le medicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Sanofi-aventis (suisse) sa is fully responsible for the accuracy and correctness of the content of this published summary RMP of Praluent®.

1. THE MEDICINE AND WHAT IT IS USED FOR

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.

PRALUENT is the active substance and it is given subcutaneously.

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 Medicine's Agency (EMA) website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/praluent

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

Important risks of PRALUENT's 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 include:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and;
- 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 PSUR 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.

2.1. 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.

Table 1 - List of important risks and missing information

Important identified risks	Immunogenicity Systemic hypersensitivity reactions
Important potential risk	Neurocognitive disorders
Missing information	Use in children and adolescents Use in pregnant and lactating women Use in patients with severe hepatic impairment Influence of alirocumab on gonadal steroid hormones and gonadotropins (in men and women)

2.2. Summary of important risks

Table 2 –Important identified risks (Immunogenicity) with corresponding risk minimizations activities and additional pharmacovigilance activities if any

Immunogenicity	
Evidence for linking the risk to the medicine	Literature, non-clinical, clinical trials
Risk factors and risk groups	No risk factors have been identified.
Risk minimization measures	Labelled in section 4.8 of the SmPC Prescription only medicine
Additional pharmacovigilance activities	None

SmPC: Summary of Product Characteristics.

Table 3 –Important identified risks (Systemic hypersensitivity reactions) with corresponding risk minimizations activities and additional pharmacovigilance activities if any

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	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

Table 4 - Important potential risks (Neurocognitive disorders) with corresponding risk minimizations activities and additional pharmacovigilance activities if any

Neurocognitive disorders	
Evidence for linking the risk to the medicine	FDA alert for statins: On 28-Feb-2012 the FDA recommended a change in the statin labeling regarding neurocognition In 2014 the FDA requested Sanofi to review neurocognitive adverse events and consider prospective testing in a long-term trial in the development program of alirocumab following observations of a potential imbalance in adverse events in another PCSK9 mAb program (see details above, in the Severity and nature of risk Section of this table). *A dedicated post-authorization Neurocognitive safety study [PASS] (R727- CL-1532) is currently ongoing (LPLV planned for 13-May-2020*). Literature: *Giugliano RP, Mach F, Zavitz K, Kurtz C, Im K, Kanevsky E, et al; EBBINGHAUS Investigators. Cognitive Function in a Randomized Trial of Evolocumab. N Engl J Med. 2017 Aug 17;377(7):633-43. (1)* A total of 1204 patients were followed for a median of 19 months as a subgroup of patients from a randomized, placebo-controlled trial of evolocumab added to statin therapy (Fourier), and had prospectively assessed cognitive function using the Cambridge Neuropsychological Test Automated Battery. In an exploratory analysis, there were no associations between LDL-C levels and cognitive changes and no significant between- group difference in cognitive function was observed over a median of 19 months. *Mefford MT, Rosenson RS, Cushman M, Farkouh ME, McClure LA, Wadley VG, et al. PCSK9 Variants and Neurocognitive Impairment: data from the reasons for geographic and racial differences in stroke (REGARDS) Study. JACC. 2017 Mar 21; 69 (11):1652.* (2) The authors found no association between PCSK9 loss-of-function variants and neurocognitive impairment as assessed by two validated measures. *Lipinski MJ, Benedetto U, Escarcega RO, Biondi-Zoccai G, Lhermusier T, Baker NC, et al. The impact of proprotein convertase subtilisin-kexin type 9 serine protease inhibitors on lipid levels and outcomes in patients with primary hypercholesterolaemia: a network meta-analysis. Eur Heart J. 2016 Feb 7;37(6):536-45.* (3)

Neurocognitive disorders	
Evidence for linking the risk to the medicine	A network meta-analysis reported that while proprotein convertase subtilisin-kexin type 9 serine protease inhibitors increased incidence of neurocognitive adverse events [Odds Ratio 2.34 (95% CI 1.11–4.93), I^2 = 4%, p = 0.02] when compared with placebo. However, a Letter to the Editor authored by the chairman of the steering committee dedicated to the alirocumab lipid-lowering studies, drew attention to the fact that the authors have not used all available and relevant clinical study data with selection of only 4 out of the 10-submitted phase 3 trials and 2 out of the 4 submitted phase 2 trials and therefore did not provide relevant results to the topic from the pooled clinical studies supporting the submission dossier (*Ginsberg HN. Eur Heart J. 2016; 37(6):536–45.* (4) *Published as eLetter*). In addition, another published comment of this paper (5) pointed out that the conclusions from this meta-analysis were based on only 55 neurocognitive events, and thus need to be considered with caution. *Khan AR, Bavishi C, Riaz H, Farid TA, Khan S, Atlas M, et al. Increased Risk of Adverse Neurocognitive Outcomes With Proprotein Convertase Subtilisin-Kexin Type 9 Inhibitors. Circ Cardiovasc Qual Outcomes. 2017 Jan;10(1).* (6) This meta-analysis of PCSK9 inhibitor trials found a higher rate of neurocognitive events with PCSK9 inhibitors versus placebo in a pool of the two largest trials: the alirocumab ODYSSEY LONG TERM trial and the open-label OSLER-2 study of evolocumab. However, the authors have again not used all available and relevant clinical study data, and more importantly have combined data from 2 studies with different methodology, double-blind for alirocumab and open-label for evolocumab.
Risk factors and risk groups	Unknown
Risk minimization measures	Prescription only medicine
Additional pharmacovigilance activities	A trial with a dedicated prospective assessment of neurocognitive function (R727-CL-1532)

CI: Confidence Interval; FDA: Food and Drug Administration; LDL-C: Low Density Lipoprotein Cholesterol; LPLV: Last Patient Last Visit; mAb: Monoclonal Antibody; PASS: Post-Authorization Safety Study; PCSK9: Pro-Protein Convertase Subtilisin Kexin type 9.

Table 5 –Missing information (Use in children and adolescents) with corresponding risk minimizations activities and additional pharmacovigilance activities if any

Use in children and adolescents	
Risk minimization measures	Labelled in section 4.2 of SmPC Labelled in section 2 of PL Prescription only medicine
Additional pharmacovigilance activities	A PIP including 3 studies is in place o DFI14223: Pediatric Phase 2 Dose finding study o EFC14643 and EFC14660: pediatric phase 3 study

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

Table 6 – Missing information (Use in pregnant and lactating women) with corresponding risk minimizations activities and additional pharmacovigilance activities if any

Use in pregnant and lactating women	
Risk minimization measures	Labelled in section 4.6 of SmPC Labelled in section 2 of PL
Additional pharmacovigilance activities	None

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

Table 7 – Missing information (Use in patients with severe hepatic impairment) with corresponding risk minimizations activities and additional pharmacovigilance activities if any

Use in patients with severe hepatic impairment	
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.

Table 8 – Missing information (Influence of alirocumab on gonadal steroid hormones and gonadotropins [in men and women]) with corresponding risk minimizations activities and additional pharmacovigilance activities if any

Influence of alirocumab on gonadal steroid hormones and gonadotropins (in men and women)	
Risk minimization measures	Prescription only medicine
Additional pharmacovigilance activities	Post authorization safety study trial with a dedicated prospective assessment of neurocognitive function (R727-CL-1532).

2.3. Post-authorization development plan

2.3.1. Studies which are conditions of the marketing authorization

Not applicable. There are no studies which are conditions of the marketing authorization or specific obligations for alirocumab.

2.3.2. Other studies in post-authorization development plan

Table 9 - Other studies in post-authorization development plan

R727-CL-1532 **Purpose of the study:** Prospective assessment of neurocognitive function.
ALIROC07997 **Purpose of the study:** Monitor muscle events, and liver function and creatine kinase abnormalities in HIV 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.
DFI14223 (Pediatric Phase 2 study) **Purpose of the study:** Evaluate the effect of alirocumab administered every 2 weeks or every 4 weeks on LDL-C levels after 8 weeks of treatment in heterozygous familial hypercholesterolemia.
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.
EFC14660 (Pediatric Phase 3 study) **Purpose of the study:** Evaluate the efficacy of alirocumab on LDL-C levels at Week 12 up to 48 weeks of treatment in children with homozygous familial hypercholesterolemia 8 to 17 years of age on top of background treatments.

LDL-C: Low Density Lipoprotein Cholesterol.