PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrPRALUENT®

alirocumab injection

75 mg solution for subcutaneous injection in a pre-filled pen
150 mg solution for subcutaneous injection in a pre-filled pen
300 mg solution for subcutaneous injection in a pre-filled pen

Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture

ATC Code: C10AX14

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS, 1.1 Pediatrics	01/2022
4 DOSAGE AND ADMINISTRATION	05/2024
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACAKGING	05/2024

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Prevention of Cardiovascular Events

PRALUENT (alirocumab injection) is indicated in combination with a maximum tolerated dose of a statin, with or without other lipid lowering therapies, to reduce the risk of myocardial infarction, ischemic stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease.

Primary Hyperlipidemia

PRALUENT (alirocumab injection) is indicated for the reduction of low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia (heterozygous familial and non-familial):

- As an adjunct to diet and statin therapy, with or without other lipid-lowering therapies;
- As an adjunct to diet, as monotherapy or in combination with other non-statin lipid-modifying therapies, in patients for whom a statin is contraindicated.

1.1 Pediatrics

The efficacy and safety of Praluent in these patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

In primary hypercholesterolemia controlled studies, 1158 patients (34.7 %) treated with PRALUENT were ≥ 65 years of age, including 241 patients (7.2 %) ≥ 75 years of age. In the cardiovascular outcomes study, 2505 patients (26.5%) treated with PRALUENT were ≥ 65 years of age, including 493 patients (5.2%) ≥ 75 years of age. No overall differences in safety or efficacy were observed between these patients and younger patients (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

- Praluent is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see the 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the product monograph.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

The recommended starting dose of Praluent is 75 mg once every 2 weeks (Q2W)-administered subcutaneously, since the majority of patients achieve sufficient LDL-C reduction with this dosage. Alternatively, 300 mg once every 4 weeks (monthly) may be administered subcutaneously for patients who prefer less frequent dosing.

Measure LDL-C levels within 4 to 8 weeks of initiating Praluent to assess response and adjust the dose, if needed. For patients receiving Praluent 300 mg every 4 weeks, measure LDL-C just prior to the next scheduled dose of initiating Praluent, since LDL-C levels in some patients can vary considerably between doses with this regimen (see 14 CLINICAL TRIALS, CHOICE I study).

If the LDL-C response is inadequate, the dosage may be adjusted to the maximum dosage of 150 mg administered every 2 weeks.

Special Populations

Pediatric patients
The efficacy and safety of Praluent in these patients have not been established (see 1 INDICATIONS, 1.1 Pediatrics)

Elderly patients
No dose adjustment is needed for elderly patients.

Hepatic impairment
No dose adjustment is needed for patients with mild or moderately impaired hepatic function. No data are available in patients with severe hepatic impairment (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Renal impairment
No dose adjustment is needed for patients with mild or moderately impaired renal function. No data are available in patients with severe renal impairment (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions – Renal Insufficiency).

Body weight
No dose adjustment is needed in patients based on weight (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions – Obesity).

4.4 Administration

Praluent is administered as a subcutaneous injection into the thigh, abdomen, or upper arm, using a single-use pre-filled pen.

To allow the solution to come to room temperature, remove the 75 mg or 150 mg pen from the refrigerator approximately 30 to 40 min before the injection, or the 300 mg pen approximately 45 minutes before the injection.

The patient may either self-inject alirocumab, or a caregiver may administer alirocumab, after guidance has been provided by a healthcare professional on proper subcutaneous injection technique.

To administer the 300 mg dose, give either one 300 mg Praluent injection or two 150 mg Praluent injections consecutively at two different injection sites. The 300 mg dose may be self-administered in thigh or abdomen. Only upper arm administrations require the help of a caregiver.

It is recommended to rotate the injection site with each injection.

Praluent should not be injected into areas of active skin disease or injury, such as sunburns, skin rashes, inflammation, or skin infections.

Do not co-administer Praluent with other injectable drugs at the same injection site.

4.5 Missed Dose

If an every 2-week dose is missed, the patient should administer the injection as soon as possible (within 7 days from the missed dose), and thereafter resume treatment two weeks from the day of the missed dose, keeping the patient's original schedule. If the missed dose is not administered within 7 days, instruct the patient to wait until the next dose on the original schedule.

If an every 4-week dose is missed, instruct the patient to administer the injection within 7 days of the missed dose and then resume the patient's original schedule. If the missed dose is not administered within 7 days, instruct the patient to administer the dose, starting a new schedule based on this date.

5 OVERDOSAGE

In controlled clinical studies, no safety issues were identified with more frequent Praluent dosing than the recommended Q2W dosing schedule.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous injection	Solution in Pre-filled Pen (PFP) 75 mg/mL 150 mg/mL 300 mg/2 mL	Histidine, polysorbate 20, sucrose, water for injection

Praluent is a clear, colourless to pale yellow solution, with a pH of about 6.0.

Praluent is supplied as a sterile, preservative-free solution for injection, in a single-use pre-filled pen (PFP).

- 75 mg/mL PFP: The syringe components are assembled into a single-use pre-filled pen with a blue cap and a light green activation button.

- 150 mg/mL PFP: The syringe components are assembled into a single-use pre-filled pen with a blue cap and a dark grey activation button.

- 300 mg/2 mL PFP: The syringe components are assembled into a single-use pre-filled pen with a blue cap and no activation button.

Each 1 mL PFP contains 75 mg or 150 mg alirocumab. Each 2 mL PFP contains 300 mg alirocumab.

Each 75 mg/mL, 150 mg/mL and 300 mg/2 mL PFP contains histidine, sucrose, polysorbate 20, and water for injection (USP), to pH 6.0.

Praluent 75 mg/mL or 150 mg/mL solution for injection in single-use PFP is supplied in a siliconized 1 mL or 2 mL Type 1 clear glass syringe. The rubber needle shield does not contain natural latex.

Pack size of 75 or 150 mg PFP: 1, 2, or 6 per carton.

Pack size of 300 mg PFP: 1 or 3 per carton.

7 WARNINGS AND PRECAUTIONS

Hepatic/Biliary/Pancreatic

Hepatic Impairment:
The safety and efficacy of Praluent in patients with severe hepatic impairment have not been studied (see 8 ADVERSE REACTIONS).

Immune

Hypersensitivity reactions (e.g., pruritus, rash, urticaria), including serious allergic reactions (i.e., angioedema, hypersensitivity reactions requiring hospitalization, nummular eczema, hypersensitivity vasculitis) have been reported with Praluent treatment (see 8 ADVERSE REACTIONS). If signs or symptoms of serious allergic reactions occur, discontinue treatment with Praluent and initiate appropriate treatment according to standard of care, and monitor until signs and symptoms resolve (see 2 CONTRAINDICATIONS).

Renal

Renal Impairment:
The safety and efficacy of Praluent in patients with severe renal impairment, including end-stage renal disease, have not been studied.

Reproductive Health: Female and Male Potential

- **Fertility**
  No data are available on the effect of Praluent on human fertility. Animal studies did not show any effects on fertility endpoints (see 16 NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 Pregnant Women

No studies have been conducted with Praluent in pregnant women and data from clinical use are very limited.

Studies in monkeys showed that alirocumab crosses the placental barrier and is pharmacologically active in infants exposed during organogenesis through parturition. A suppression of the humoral immune response to keyhole limpet hemocyanin (KLH) antigen was observed in offspring of exposed animals. Animal studies did not demonstrate any additional effects on pregnancy or neonatal/infant development (see 16 NON-CLINICAL TOXICOLOGY).

Animal studies are not always predictive of human response. Therefore, it is not known whether Praluent can cause fetal harm when administered to a pregnant woman. Praluent is used in combination with maximally tolerated statin. Statin Product Monographs recommend discontinuation when a patient becomes pregnant, therefore Praluent should also be discontinued (see the Special Populations section of the relevant statin Product Monograph).

7.1.2 Breast-feeding

There is no information regarding the presence of Praluent in human breast milk, the effects on the breastfed infant, or the effects on milk production. A risk to breastfed newborns and infants cannot be excluded. Because many drugs and immunoglobulins are excreted in human milk, the use of Praluent is not recommended in breastfeeding women.

7.1.3 Pediatrics

The efficacy and safety of Praluent in pediatric patients have not been established (see 1 INDICATIONS, 1.1 Pediatrics); therefore, Health Canada has not authorized an indication for pediatric use. Clinical trial experience in the pediatric population is limited to 8 patients aged 9-11 (<12) years and 10 patients aged 12-17 (≥12-<18) years with homozygous familial hypercholesterolemia (HoFH), treated with 75mg (BW<50kg) or 150mg (BW>50kg) of PRALUENT Q2W for up to 48 weeks. No data are available in patients younger than 9 years of age.

7.1.4 Geriatrics

In controlled studies, 1158 patients (34.7 %) treated with Praluent were ≥ 65 years of age and 241 patients (7.2 %) treated with Praluent were ≥ 75 years of age. No overall differences in safety or efficacy were observed between age classes but data are limited in patients over 75 years of age.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety data described below reflect exposure to Praluent in 2476 patients (2758.5 patient-years of exposure), the majority with high or very high cardiovascular risk, treated with Praluent at a dose of 75 or 150 mg, administered subcutaneously once every 2 weeks (Q2W), for a treatment duration of up to 18 months (including 1999 patients exposed to Praluent for at least 52 weeks, and 639 patients

exposed to Praluent for at least 76 weeks). The safety data are based on pooled results from nine placebo-controlled studies (four phase 2 and five phase 3 studies, all in patients on background statin).

Serious adverse events occurred in 13.7% of patients treated with Praluent and 14.3% of patients in the placebo group.

In ten phase 3 controlled trials, involving patients with primary hypercholesterolemia, the most common adverse reactions were local injection site reactions (including erythema/redness, itching, swelling, pain/tenderness), upper respiratory tract signs and symptoms and pruritus (itch). Adverse reactions led to discontinuation of treatment in 5.3% of patients treated with Praluent and 5.1% of patients in the placebo group. The most common adverse reactions leading to treatment discontinuation in patients treated with Praluent were allergic reactions (0.6% versus 0.2% for Praluent and placebo, respectively) and injection site reactions (0.2% versus 0.4% for Praluent and placebo, respectively).

The safety profile of Praluent derived from the cardiovascular outcomes study (ODYSSEY OUTCOMES) was consistent with the overall safety profile described in the phase 3 controlled trials.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 2 – Adverse Events Occurring in ≥ 1% of Patients Treated with Praluent and More Frequently than with Placebo in the Pool of 10 Hyperlipidemia Placebo-Controlled Trials

System Organ Class Preferred Term*	Placebo (N=1276)	Alirocumab (N=2476)
Cardiac disorders		
Angina unstable	0.9%	1.2%
Gastrointestinal disorders		
Diarrhoea	4.4%	4.7%
Constipation	1.5%	1.7%
Abdominal pain	1.3%	1.6%
Abdominal pain upper	0.8%	1.1%
General disorders and administration site conditions		
Injection site reaction	5.1%	7.2%
Oedema peripheral	0.9%	1.3%
Infections and infestations		
Nasopharyngitis	11.1%	11.3%

System Organ Class Preferred Term*	Placebo (N=1276)	Alirocumab (N=2476)
Influenza	4.6%	5.7%
Urinary tract infection	4.6%	4.8%
Bronchitis	3.8%	4.3%
Sinusitis	2.7%	3.0%
Gastroenteritis viral	0.7%	1.3%
Pneumonia	1.1%	1.3%
Pharyngitis	0.8%	1.1%
Cellulitis	0.8%	1.0%
Injury, poisoning and procedural complications		
Contusion	1.3%	2.1%
Investigations		
Alanine aminotransferase increased	0.7%	1.1%
Metabolism and nutrition disorders		
Diabetes mellitus	1.1%	1.3%
Type 2 diabetes mellitus	0.9%	1.3%
Gout	0.9%	1.1%
Musculoskeletal and connective tissue disorders		
Myalgia	3.4%	4.2%
Muscle spasms	2.4%	3.1%
Musculoskeletal pain	1.6%	2.1%
Psychiatric disorders		
Insomnia	1.3%	1.4%
Respiratory, thoracic and mediastinal disorders		
Cough	2.3%	2.5%
Oropharyngeal pain	0.5%	1.2%
Skin and subcutaneous tissue disorders		
Pruritus	0.4%	1.1%
Vascular disorders		
Hypertension	3.0%	3.1%

System Organ Class Preferred Term*	Placebo (N=1276)	Alirocumab (N=2476)

* coded using MedDRA version 17.0

The safety profile of alirocumab in the ezetimibe-controlled studies (COMBO II, MONO, ALTERNATIVE) was consistent with the safety profile in the placebo-controlled studies with no additional adverse reactions identified.

Table 3 – Adverse Events Occurring in > 1% of Patients Treated with Praluent and More Frequently than with Placebo in the Cardiovascular Outcomes Study (ODYSSEY OUTCOMES)

System Organ Class Preferred Term*	Placebo (N=9443)	Alirocumab (N=9451)
Any class	77.1%	75.8%
Ear and labyrinth disorders		
Vertigo	1.3%	1.4%
Gastrointestinal disorders		
Nausea	1.8%	2.1%
Gastrooesophageal reflux disease	1.4%	1.7%
Abdominal pain upper	1.3%	1.4%
General disorders and administration site conditions		
Non-cardiac chest pain	6.8%	7.0%
Injection site reaction	1.4%	2.8%
Infections and infestations		
Nasopharyngitis	5.6%	6.0%
Sinusitis	1.3%	1.5%
Lower respiratory tract infection	1.0%	1.1%
Injury, poisoning and procedural complications		
Contusion	1.7%	1.8%
Musculoskeletal and connective tissue disorders		
Myalgia	5.3%	5.6%
Back pain	4.2%	4.3%
Arthralgia	3.7%	3.9%
Muscle spasms	2.1%	2.3%

System Organ Class Preferred Term*	Placebo (N=9443)	Alirocumab (N=9451)
Nervous system disorders		
Hypoaesthesia	0.9%	1.0%
Psychiatric disorders		
Insomnia	1.3%	1.5%
Reproductive system and breast disorders		
Benign prostatic hyperplasia	1.2%	1.3%
Erectile dysfunction	0.9%	1.0%
Skin and subcutaneous tissue disorders		
Rash	1.1%	1.2%
Vascular disorders		
Hypotension	1.8%	1.9%

* coded using MedDRA version 20.1

Injection site reactions
Injection site reactions, including erythema/redness, itching, swelling, and pain/tenderness were reported in 7.2% of patients treated with Praluent vs. 5.1% in the placebo group. Most injection site reactions were transient and of mild intensity. The discontinuation rate due to local injection site reactions was 0.2% versus 0.4% for Praluent and placebo, respectively.

In a 48-week placebo-controlled trial evaluating injection of Praluent 300 mg every 4 weeks (Q4W) or 75 mg every 2 weeks (Q2W) , in which all patients received an injection of drug or placebo every 2 weeks to maintain the blind (see 14 CLINICAL TRIALS, CHOICE I study), local injection site reactions were reported more frequently in patients treated with Praluent 300 mg Q4W as compared to those receiving Praluent 75 mg Q2W or placebo (16.6%, 9.6%, and 7.9%, respectively). The discontinuation rate due to injection site reactions was 0.7% in patients treated with Praluent 300 mg Q4W versus 0% in the placebo treatment group.

In the cardiovascular outcomes study (ODYSSEY OUTCOMES), injection site reactions also occurred more frequently in alirocumab-treated patients than in placebo-treated patients (3.8% alirocumab versus 2.1% placebo).

Allergic reactions
General allergic reactions were reported more frequently in the Praluent group than in the placebo group (8.6% vs 7.8% respectively), mainly due to a difference in the incidence of pruritus. The proportion of patients who discontinued treatment due to allergic reactions was higher among those

treated with Praluent (0.6% versus 0.2%). In addition, rare and sometimes serious allergic reactions, such as hypersensitivity, nummular eczema, and hypersensitivity vasculitis have been reported in controlled clinical studies.

Neurocognitive Events
Neurocognitive events were reported in 0.8% of patients treated with Praluent and 0.7% of the placebo group patients. Confusion or memory impairment were each reported in 0.2% of patients treated with Praluent and in <0.1% (for each) in the placebo group patients. The majority of neurocognitive events were non-serious. See 14 CLINICAL TRIALS for the results of the Neurocognitive Function study (R727-CL-1532).

Liver Enzyme Abnormalities
Hepatic abnormalities (primarily related to abnormalities in liver enzymes) were reported in 2.5% of patients treated with Praluent and 1.8% of the placebo group patients. Increases in serum alanine transaminase (ALT) to greater than 3 times the upper limit of normal occurred in 1.7% of patients treated with Praluent and 1.4% of the placebo group patients.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity.

In the ODYSSEY OUTCOMES trial, 5.5% of patients treated with alirocumab 75 mg and/or 150 mg every 2 weeks (Q2W) had anti-drug antibodies (ADA) detected after initiating treatment compared with 1.6% of patients treated with placebo. Persistent ADA responses were observed in 0.7% of patients treated with alirocumab and 0.4% of patients treated with placebo. Neutralizing antibody (NAb) responses were observed in 0.5% of patients treated with alirocumab and in <0.1% of patients treated with placebo.

Anti-drug antibody responses, including NAb, were low titer and did not appear to have a clinically meaningful impact on the efficacy or safety of alirocumab, except for a higher rate of injection site reactions in patients with treatment emergent ADA compared to patients who were ADA negative (7.5% vs 3.6%). The long-term consequences of continuing alirocumab treatment in the presence of ADA are unknown.

In a pool of ten placebo-controlled and active-controlled trials of patients treated with alirocumab 75 mg and/or 150 mg Q2W as well as in a separate clinical study of patients treated with alirocumab 75 mg Q2W or 300 mg every 4 weeks (including some patients with dose adjustment to 150 mg Q2W), the incidence of detecting ADA and NAb was consistent with the results from the ODYSSEY OUTCOMES trial.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay as well as other factors. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to alirocumab with the incidence of antibodies to other products may be misleading.

Low LDL-C levels
In the pool of the placebo- and active-controlled studies using an every 2 week or every 4 week dosing interval, 914 of 3913 patients (23.4 %) treated with Praluent had two consecutive values of LDL-C <0.65

mmol/L (25 mg/dL), including 335 patients (8.6 %) with two consecutive values of LDL-C <0.39 mmol/L (15 mg/dL). LDL-C values < 0.65 mmol/L (25 mg/dL) and <0.39 mmol/L (15 mg/dL) were observed more frequently in patients treated with the Praluent 150 mg Q2W or 300 mg Q4W dosing regimens.

Although adverse consequences of very low LDL-C were not identified in alirocumab trials, the long-term effects of sustained very low levels of LDL-C are unknown.

8.3 Less Common Clinical Trial Adverse Reactions

In the pooled placebo- and ezetimibe-controlled studies, the following adverse reactions were observed with a frequency of less than 1% and at a higher frequency in the Praluent arm compared to control (control vs. Praluent):

***Blood and lymphatic system disorders*:** neutropenia (<0.1% vs. 0.2%)

***Cardiac disorders*:** palpitations (<0.1% vs. 0.2%)

***Gastrointestinal disorders*:** abdominal pain (0.1% vs. 0.2%), constipation (0.1% vs. 0.2%)

***General disorders and administration site conditions*:** fatigue (0.5% vs. 0.6%), asthenia (0.1% vs. 0.3%), injection site erythema (<0.1% vs. 0.1%)

***Immune system disorders*:** hypersensitivity (0.1% vs. 0.2%)

***Infections and infestations*:** urinary tract infection (0% vs. 0.1%)

***Injury, poisoning and procedural complications*:** accidental overdose (0.5% vs. 0.6%)

***Investigations*:** alanine aminotransferase increased (0.3% vs. 0.4%), gamma-glutamyltransferase increased (<0.1% vs. 0.1%)

***Metabolism and nutrition disorders*:** decreased appetite (<0.1% vs. 0.1%)

***Musculoskeletal and connective tissue disorders*:** muscle spasms (0.4% vs. 0.6%)

***Nervous system disorders*:** hypoesthesia (<0.1% vs. 0.2%)

***Respiratory, thoracic and mediastinal disorders*:** epistaxis (<0.1% vs. 0.1%)

***Skin and subcutaneous tissue disorders*:** pruritus (0.1% vs. 0.3%), rash (0.1% vs. 0.3%)

8.5 Post-Market Adverse Reactions

The following additional adverse reactions have been reported during post-market use of Praluent.

General disorders and administration site conditions
Flu-like illness

Skin and subcutaneous tissue disorders
Angioedema

9 DRUG INTERACTIONS

9.1 Drug Interactions Overview

No formal drug-drug interaction studies have been conducted for alirocumab, nor have any studies been conducted to assess interactions with food/diet, herbal products or lifestyle.

9.2 Drug- Behavioural Interactions

Interactions with behaviour have not been established.

9.3 Drug-Drug Interactions

Effects of alirocumab on other drugs
In clinical studies where alirocumab was administered in combination with atorvastatin or rosuvastatin, no relevant changes in statin concentrations were observed in the presence of repeated administration of alirocumab.

9.4 Drug- Food Interactions

Interactions with food have not been established.

9.5 Drug- Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug- Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Alirocumab is a fully human monoclonal antibody (Immunoglobulin IgG1 isotype) that binds with high affinity and specificity to proprotein convertase subtilisin kexin type 9 (PCSK 9). Alirocumab is produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture.

PCSK9 binds to the low-density lipoprotein receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. LDLR is the primary receptor that clears circulating LDL, therefore the decrease in LDLR levels by PCSK9 results in higher blood levels of LDL-C. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs available to clear LDL, thereby lowering LDL-C levels.

10.2 Pharmacodynamics

Alirocumab reduced free PCSK9 in a concentration-dependent manner. Following a single subcutaneous administration of alirocumab 75 or 150 mg, maximal suppression of free PCSK9 occurred within 4 to 8 hours. Free PCSK9 concentrations returned to baseline when alirocumab concentrations decreased below the limit of quantitation.

10.3 Pharmacokinetics

Table 4 – Summary of alirocumab pharmacokinetic parameters in adults with established cardiovascular disease, and primary hyperlipidemia (heterozygous familial and non-familial)

Dose Regimen	C_{max} (mg/L)	Tmax[a] (day)	t½ (day)	$AUC_{0-\infty}$ (day*mg/L)	CL/F (L/day)	Vz/F (L)
75 mg	8.18 ± 2.51 [30.7]	2.96 (1.95 - 7.01)	6.03 ± 1.11 [18.5]	129 ± 35.7 [27.8]	0.627 ± 0.175 [27.9]	5.52 ± 2.15 [39.1]
150 mg	14.6 ±7.95 [54.5]	7.00 (3.00-7.94)	7.64 ± 1.96 [25.7]	293 ±172 [58.6]	0.690 ±0.404 [58.6]	7.76 ±5.63 [72.6]
300 mg	29.9 ± 7.76 [25.9]	5.00 (2.00 - 7.00)	8.81 ± 5.50 [62.4]	678 ± 231 [34.1]	0.512 ± 0.262 [51.2]	5.16 ± 2.38 [46.1]

[a]: Median (Min-Max)

Absorption
After subcutaneous (SC) administration of 75 mg to 300 mg alirocumab, median times to maximum serum concentration (t_{max}) were 3-7 days.

The pharmacokinetics (PK) of alirocumab after single SC administration of 75 mg into the abdomen, upper arm or thigh were similar.

The absolute bioavailability of alirocumab after SC administration was about 85% as determined by population PK analysis.

A slightly greater than dose proportional increase was observed, with a 2.1- to 2.7-fold increase in total alirocumab concentrations for a 2-fold increase in dose from 75 mg every 2 weeks to 150 mg every 2 weeks. Monthly exposure with 300 mg every 4 weeks treatment was similar to that of 150 mg every 2 weeks.

Steady state was reached after 2 to 3 doses with an accumulation ratio up to a maximum of about 2-fold.

Distribution
Following IV administration, the volume of distribution was about 0.04 to 0.05 L/kg indicating that alirocumab is distributed primarily in the circulatory system.

Metabolism
Specific metabolism studies were not conducted, because alirocumab is a protein. Alirocumab is expected to degrade to small peptides and individual amino acids.

Elimination
Two elimination phases were observed for alirocumab. At low concentrations, the elimination is predominately through saturable binding to target (PCSK9), while at higher concentrations the elimination of alirocumab is largely through a non-saturable proteolytic pathway.

Based on a population pharmacokinetic analysis, the median apparent half-life of alirocumab at steady state was 17 to 20 days in patients receiving alirocumab at subcutaneous doses of 75 mg Q2W or 150 mg Q2W. When co-administered with a statin, the median apparent half-life of alirocumab was reduced to 12 days.

Special Populations and Conditions

- **Pediatrics**
  The pharmacokinetic profile of alirocumab has not been established in pediatric patients (see 1 INDICATIONS, 1.1 Pediatrics). Health Canada has not authorized an indication for pediatric use.

- **Geriatrics**
  Based on a population pharmacokinetic analysis, age was associated with a small difference in alirocumab exposure at steady state, with no impact on efficacy or safety.

- **Sex**
  Based on a population pharmacokinetic analysis, gender was found not to significantly influence alirocumab pharmacokinetics

- **Ethnic Origin**
  Based on a population pharmacokinetic analysis, race was found not to significantly influence alirocumab pharmacokinetics.

- **Hepatic Insufficiency**
  In a phase 1 study, after administration of a single 75 mg SC dose, alirocumab pharmacokinetic profiles in subjects with mild and moderate hepatic impairment were similar as compared to subjects with normal hepatic function. No data are available in patients with severe hepatic impairment.

- **Renal Insufficiency**
  Since monoclonal antibodies are not known to be eliminated via renal pathways, renal function is not expected to impact the pharmacokinetics of alirocumab. No data are available in patients with severe renal impairment.

- **Obesity**
  Based on a population pharmacokinetic analysis, body weight was associated with a small difference in alirocumab exposure, with no significant influence on efficacy or safety.

11 STORAGE, STABILITY AND DISPOSAL

Store in a refrigerator at 2°C to 8°C (36°to 46° F). Do not freeze.

Store in the outer carton in order to protect from light.

Do not expose to extreme heat.

12 SPECIAL HANDLING INSTRUCTIONS

The patient may either self-inject Praluent, or a caregiver may administer Praluent, after guidance has been provided by a health professional on proper subcutaneous injection technique.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. If the solution is discoloured or contains visible particulate matter, the solution should not be used.

The 75 mg/mL or 150 mg/mL pre-filled pen (PFP) should be allowed to warm to room temperature for 30-40 minutes prior to use. The 300 mg/2 mL PFP should be allowed to warm to room temperature for 45 minutes prior to use. Praluent should be used as soon as possible after it has warmed up. Time out of refrigeration should not exceed 30 days at 25°C.

After use, place the PFP into a puncture-resistant container and discard as required by local (provincial) regulations. Do not recycle the container. Always keep the container out of the reach of children.

Patients and caregivers should receive guidance on proper subcutaneous injection technique, including aseptic technique, and how to use the PFP correctly (see Instructions for Use leaflet).

Patients and caregivers should be reminded to read the patient information leaflet and Instructions for Use leaflet carefully before administration of Praluent.

Patients and caregivers should be cautioned that the PFP must not be re-used, and instructed on how to safely discard after use.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Proper name: Alirocumab

Molecular mass: 146 kDa

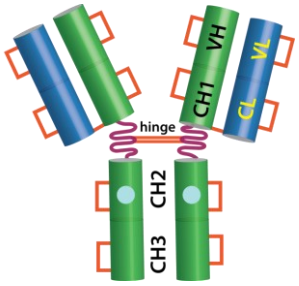
Physicochemical properties: Alirocumab is a sterile, preservative-free, clear, colourless to pale yellow solution for subcutaneous injection

Drug Substance

Alirocumab is a fully human monoclonal antibody (IgG1 isotype) that targets proprotein convertase subtilisin kexin type 9 (PCSK 9). Alirocumab is produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture.

Alirocumab consists of two disulfide-linked human heavy chains, each covalently linked through a disulfide bond to a fully human kappa light chain. A single N-linked glycosylation site is located in each heavy chain within the CH2 domain of the Fc constant region of the molecule. The variable domains of the heavy and light chains combine to form the PCSK9 binding site within the antibody. Alirocumab has an approximate molecular weight of 146 kDa.

Figure 1 – Schematic Representation of the Structure of Alirocumab*



* Orange= Location of intra-chain and inter-chain disulfide bonds; Green=Heavy chains; Blue=Light chains; Cyan= Fc domain glycosylation site; CH = constant region of the heavy chain; CL = constant region of the light chain; VH = variable region of the heavy chain; VL = variable region of the light chain.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Prevention of Cardiovascular Events

Table 5 – Summary of Trial Design and Patient Demographics for Prevention of Cardiovascular Events

Study	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
Cardiovascular outcomes trial					
OUTCOMES	Multicentre, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effect of alirocumab on the occurrence of cardiovascular events in patients who have recently experienced an acute coronary syndrome	In addition to maximally tolerated daily statin therapy ± other LMT*: - Alirocumab 75 mg Q2W, with up-titration to 150 mg Q2W if needed[#] - Placebo 5 years	Alirocumab: 9462 Placebo: 9462	Overall: 58.6y (39-92) Alirocumab: 58.5y (40-90) Placebo: 58.6y (39-92)	Overall: 74.8% M/25.1% F Alirocumab: 74.7% M/25.3% F Placebo: 74.9% M/25.1% F

[#] Dose up-titration of alirocumab to 150 mg Q2W occurred at month 2 in patients with LDL-C ≥ 1.29 mmol/L (50 mg/dL)

*LMT: lipid-modifying therapy

Study demographics and trial design

The cardiovascular outcomes study (ODYSSEY OUTCOMES) was a multicentre, double-blind, placebo-controlled, event-driven trial, which included 18,924 adult patients (9462 alirocumab; 9462 placebo) that were followed for a median duration of 33 months (24 months to 5 years). Patients had experienced an acute coronary syndrome (ACS) event 4 to 52 weeks prior to randomization and were treated with a lipid-modifying-therapy (LMT) regimen that was statin-intensive (i.e., atorvastatin 40 or 80 mg, or rosuvastatin 20 or 40 mg or at maximally tolerated dose of those statins) with or without other LMT.

All patients were randomized 1:1 to receive either Praluent 75 mg once every two weeks (Q2W) or placebo Q2W. At month 2, if additional LDL-C lowering was required based on pre-specified LDL-C criteria (LDL-C ≥1.29 mmol/L), Praluent was adjusted to 150 mg Q2W. For patients who had their dose adjusted to 150 mg Q2W and who had two consecutive LDL-C values below 0.65 mmol/L, down-titration from 150 mg Q2W to 75 mg Q2W was performed. Patients receiving 75 mg Q2W who had two consecutive LDL-C values below 0.39 mmol/L were switched to placebo in a blinded fashion. In total, 2615 (27.7%) patients receiving Praluent required dose adjustment to 150 mg Q2W; 805 (30.8%) subsequently were down-titrated to 75 mg Q2W. Overall, 730 (7.7%) patients receiving Praluent were switched to placebo. A total of 99.5% of patients were followed for survival until the end of the trial.

The primary efficacy endpoint was the time from randomization to first occurrence of one of the following clinical events, as determined by the Clinical Events Committee: coronary heart disease (CHD) death (including "undetermined causes of death"), any non-fatal myocardial infarction (MI), fatal and non-fatal ischemic stroke (including "stroke not otherwise specified"), and unstable angina (UA) requiring hospitalization. The final analysis was scheduled to occur when 1613 events had occurred or 24 months after the last date of randomization (excluding China), whichever occurred last.

The index ACS event was a myocardial infarction in 83.2% of patients (34.6% STEMI, 48.6% NSTEMI) or an episode of unstable angina in 16.8% of patients. Prior to the index ACS event, 19.2% of patients had a myocardial infarction and 22.7% had coronary revascularization procedures (CABG/PCI). Most patients (88.8%) were receiving high intensity statin therapy with or without other LMT at randomization. The mean LDL-C value at baseline was 2.39 mmol/L; a total of 28.8% of patients had diabetes at baseline.

Praluent significantly reduced the risk of the primary composite endpoint: time-to-first occurrence of coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), fatal and non-fatal ischemic stroke, or unstable angina (UA) requiring hospitalization (p =0.0003) (see Table 6).

Table 6 – Efficacy of Praluent in Patients with Established Cardiovascular Disease (ITT Population)

Endpoint	Number of patients with an event n (%)		Hazard Ratio[a] (95% CI)	p-value[b]
	Placebo N=9462	Praluent N=9462		
Primary composite endpoint[c]	1052 (11.1)	903 (9.5)	0.85 (0.78, 0.93)	0.0003
Coronary Heart Disease Death	222 (2.3)	205 (2.2)	0.92 (0.76, 1.11)	
Myocardial Infarction[d]	722 (7.6)	626 (6.6)	0.86 (0.77, 0.96)	
Ischemic Stroke[d]	152 (1.6)	111 (1.2)	0.73 (0.57, 0.93)	
Unstable Angina Requiring Hospitalization[d]	60 (0.6)	37 (0.4)	0.61 (0.41, 0.92)	
All-cause Mortality[e]	392 (4.1)	334 (3.5)	0.85 (0.73, 0.98)	

a Cox Proportional Hazard model with treatment as a factor and stratified by geographical region

b Two-sided log-rank test stratified by geographical region

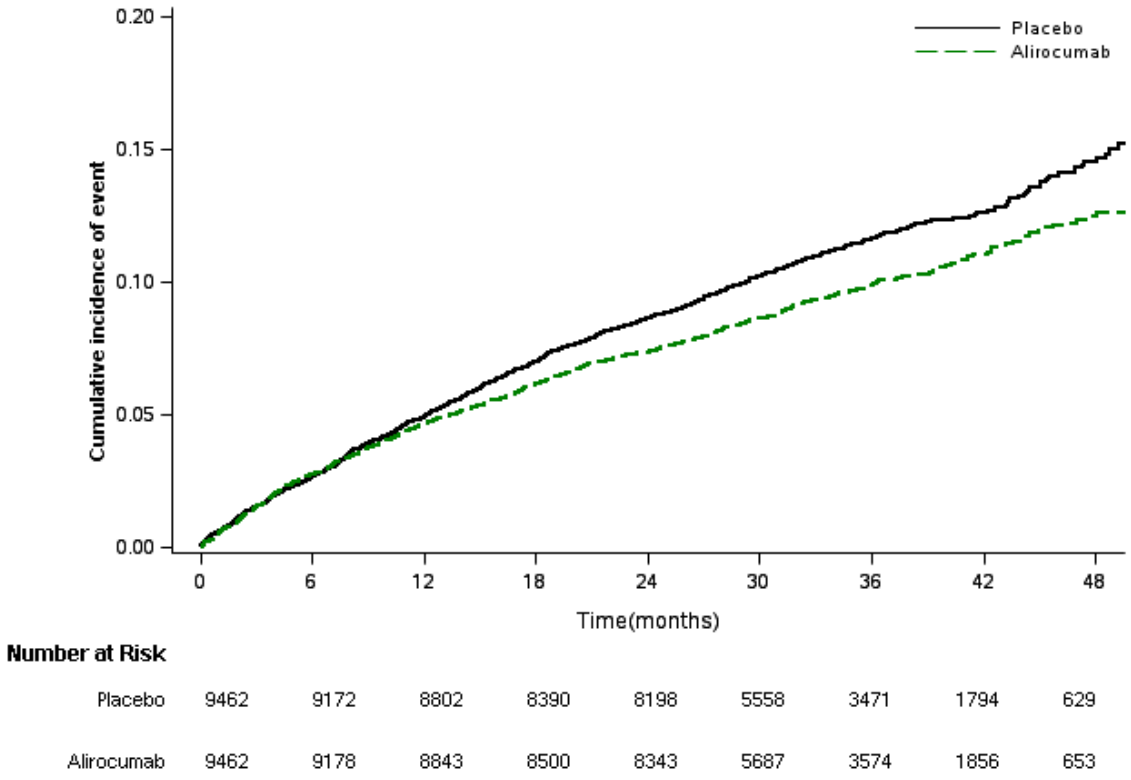
c MACE defined as a composite of coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), fatal and non-fatal ischemic stroke, or unstable angina (UA) requiring hospitalization

d Statistical testing performed outside hierarchy; therefore not considered statistically significant

e Not statistically significant per pre-specified method to control for type I error.

The Kaplan-Meier estimates of the cumulative incidence of the primary endpoint over time for the overall patient population is presented in Figure 2.

Figure 2 – Major Atherosclerotic Cardiovascular Disease Events: Cumulative Incidence Over 4 Years in ODYSSEY OUTCOMES



Primary Hyperlipidemia

Table 7 – Summary of Trial Design and Patient Demographics in Primary Hyperlipidemia

Study	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
Placebo-controlled trials					
LONG TERM	Multicentre, randomized, double-blind, placebo-controlled, in patients with HeFH** or non-FH[≠]	In addition to stable maximally tolerated daily statin ± other LMT*: - Alirocumab	Alirocumab: 1553 Placebo: 788	Overall: 60.5 y (18-89) Alirocumab	Overall: 62.2% M/ 37.8%F Alirocumab

Study	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
	and on a maximally tolerated dose of statin ± other LMT*	150 mg Q2W - Placebo 18 months		: 60.4 y (18-89) Placebo: 60.6 y (19-87)	: 63.3% M/ 36.7% F Placebo: 60.2% M/ 39.8% F
COMBO I	Multicentre, randomized, double-blind, placebo-controlled, in patients at high CV risk with hypercholesterolemia on a stable maximally tolerated dose of statin ± other LMT*	In addition to stable maximally tolerated daily statin ± other LMT*: - Alirocumab 75 mg Q2W, with up-titration to 150 mg Q2W if needed[§] - Placebo 52 weeks	Alirocumab: 209 Placebo: 107	Overall: 63 y (39-87) Alirocumab: 63 y (40-87) Placebo: 64 y (39-83)	Overall: 65.8% M/ 34.2% F Alirocumab: 62.7% M/ 37.3% F Placebo: 72% M/ 28% F
FH I	Multicentre, randomized, double-blind, placebo-controlled, parallel-group, in patients with HeFH** not adequately controlled with their current LMT (stable maximally tolerated daily statin therapy ± other LMT*)	In addition to stable maximally tolerated daily statin therapy ± other LMT*: - Alirocumab 75 mg Q2W, with up-titration to 150 mg Q2W if needed[§] - Placebo 18 months	Alirocumab: 323 Placebo: 163	Overall: 51.9 y (20-87) Alirocumab: 52.1 y (20-87) Placebo: 51.7 y (21-78)	Overall: 56.4% M/ 43.6% F Alirocumab: 55.7% M/ 44.3% F Placebo: 57.7% M/ 42.3% F
FH II	Multicentre, randomized, double-blind, placebo-controlled, parallel-group, in patients with HeFH** not adequately controlled with their LMT (stable maximally tolerated daily statin therapy ± other LMT*)	In addition to stable maximally tolerated daily statin therapy ± other LMT*: - Alirocumab 75 mg Q2W, with up-titration to 150 mg Q2W if needed[§] - Placebo 18 months	Alirocumab: 167 Placebo: 82	Overall: 53.2 y (22-85) Alirocumab: 53.2 y (22-85) Placebo: 53.2 y (23-84)	Overall: 52.6% M/ 47.4% F Alirocumab: 51.5% M/ 48.5% F Placebo: 54.9% M/ 45.1% F

Study	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
HIGH FH	Multicentre, randomized, double-blind, placebo-controlled, in HeFH** patients with a LDL-C ≥ 4.14 mmol/L (160 mg/dL)), not adequately controlled with their LMT* (maximum tolerated dose of statin ± other LMT*)	In addition to stable maximally tolerated daily statin therapy ± other LMT*: - Alirocumab 150 mg Q2W - Placebo 18-months	Alirocumab: 72 Placebo: 35	Overall: 50.6 y (18-80) Alirocumab: 46.8 y (18-80) Placebo: 52.1 y (25-69)	Overall: 53.3% M/ 46.7% F Alirocumab: 48.6% M/ 51.4% F Placebo: 62.9% M/ 37.1% F
CHOICE I	Multicentre, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of alirocumab Q4W in patients with primary hypercholesterolemia	Patients with or without concomitant statin therapy: - Alirocumab 300 mg Q4W, with up-titration to 150 mg Q2W if needed[¢] - Alirocumab 75 mg Q2W, with up-titration to 150 mg Q2W if needed[¢] - Placebo 48 weeks	Alirocumab 300 mg Q4W: 458 Alirocumab 75 mg Q2W: 115 Placebo: 230	Overall: 60.8y (21-88) Alirocumab 300 mg Q4W: 60.9y (21-88) Alirocumab 75 mg Q2W: 60.2y (31-83) Placebo: 60.9y (31-86)	Overall: 57.5%M/ 42.5%F Alirocumab 300 mg Q4W: 55.9% M/44.1%F Alirocumab 75 mg Q2W: 56.5% M/43.5% F Placebo: 61.3% M/38.7% F
R727-CL-1532	Randomized, double-blind, placebo-controlled study to evaluate the effect of alirocumab on neurocognitive function in patients with HeFH or non-FH, at high or very high cardiovascular risk	- Alirocumab 75 mg Q2W, with up-titration to 150 mg Q2W if needed - Placebo 96 weeks	Alirocumab: 1087 Placebo: 1084	Overall: 62.6 y (40-85) Alirocumab: 62.6 y (40-85) Placebo: 62.7 y (40-85)	Overall: 58.2% M/ 41.8% F Alirocumab: 58.8% M/ 41.2% F Placebo: 57.7% M/

Study	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
					42.3% F
Ezetimibe-controlled trials					
COMBO II	Multicentre, randomized, double-blind, ezetimibe-controlled, in patients at high CV risk with hypercholesterolemia and not at their pre-defined target LDL-C on a maximally tolerated dose of statin	In addition to statin at maximal tolerated daily dose: - Alirocumab 75mg Q2W, with up-titration to 150 mg Q2W if needed § - Ezetimibe 10 mg QD£ 2 years	Alirocumab: 479 Ezetimibe: 241	Overall: 61.6 y (29-88) Alirocumab: 61.7 y (30-88) Ezetimibe : 61.3 y (29-84)	Overall: 73.6% M/ 26.4% F Alirocumab: 75.2% M/ 24.8% F Ezetimibe : 70.5% M/ 29.5% F
ALTERNATIVE	Multicentre, randomized, double-blind, ezetimibe-controlled, in patients with moderate or high CV risk and with documented statin intolerance due to skeletal muscle-related symptoms	In addition to stable LMT* (other than statin and ezetimibe): - Alirocumab 75mg Q2W, with up-titration to 150 mg Q2W if needed ¥ - Ezetimibe 10 mg QD£ - Atorvastatin 20 mg QD£ 24 weeks	Alirocumab: 126 Ezetimibe : 125 Atorvastatin : 63	Overall: 63.4 y (31-88) Alirocumab: 64.1 y (39-85) Ezetimibe: 62.8 y (31-83) Atorvastatin: 63.4 y (42-88)	Overall: 54.8% M/ 45.2% F Alirocumab: 55.6% M/ 44.4% F Ezetimibe: 53.6% M/ 46.4% F Atorvastatin: 55.6% M/ 44.4% F
MONO	Multicentre, randomized, double-blind, ezetimibe-controlled, in patients with a moderate CV risk, not taking statins or other lipid-modifying therapies, and with a baseline LDL-C of 2.59 - 4.91 mmol/L (100-190 mg/dL)	- Alirocumab 75mg Q2W, with up-titration to 150 mg Q2W if needed § - Ezetimibe 10 mg QD£ 24 weeks	Alirocumab: 52 Ezetimibe: 51	Overall: 60.2 y (45-72) Alirocumab: 60.8 y (49-72) Ezetimibe: 59.6 y (45-69)	Overall: 53.4% M/ 46.6% F Alirocumab: 53.8% M/ 46.2% F Ezetimibe: 52.9% M/ 47.1% F

Study	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender

[#] Dose up-titration of alirocumab to 150 mg Q2W occurred at month 2 in patients with LDL-C ≥ 1.29 mmol/L (50 mg/dL)

*LMT: lipid-modifying therapy

§ Dose up-titration of alirocumab to 150 mg Q2W occurred at week 12 in patients with LDL-C ≥ 1.81 mmol/L (70 mg/dL)

¢ Dose up-titration of alirocumab to 150 mg Q2W occurred at week 12 if additional LDL-C lowering was required based on pre-specified LDL-C criteria

[¥] Dose up-titration of alirocumab to 150 mg Q2W occurred at week 12 in patients with LDL-C ≥ 1.81 mmol/L (70 mg/dL) or 2.59 mmol/L (100mg/dL) depending on their level of CV risk

£ QD: once daily

** HeFH: heterozygous familial hypercholesterolemia

[±] non-FH : non-familial hypercholesterolemia

Study demographics and trial design

The efficacy of alirocumab was investigated in five double-blind placebo-controlled phase 3 trials that enrolled 3499 patients; 36% were patients with heterozygous familial hypercholesterolemia (HeFH) and 54% were non-FH patients who had clinical atherosclerotic cardiovascular disease. Three of the five studies were conducted exclusively in patients with heterozygous familial hypercholesterolemia (HeFH). All patients were taking background lipid-modifying therapy (LMT) consisting of a maximally tolerated dose of statin, with or without other lipid-modifying therapies. In the trials that enrolled patients with HeFH, the diagnosis of HeFH was made either by genotyping or clinical criteria ("definite FH" using either the Simon Broome or WHO/Dutch Lipid Network criteria). All trials were at least 52 weeks in duration with the primary efficacy endpoint measured at week 24 (mean percent change in LDL-C from baseline).

Two studies (LONG TERM and HIGH FH), involving a total of 2416 patients, were performed with a 150 mg every 2 weeks (Q2W) dose only. Three studies (COMBO I, FH I and FH II) were performed with a dose of 75 mg Q2W, and criteria-based up-titration to 150 mg Q2W at week 12 in patients who did not achieve their pre-defined target LDL-C based on their level of CV risk at week 8.

The efficacy of Praluent was also investigated in three ezetimibe-controlled trials (COMBO II, ALTERNATIVE, MONO) using an initial dose of 75 mg Q2W followed by criteria-based up-titration to 150 mg Q2W at week 12, with the primary efficacy endpoint measured at week 24 (mean percent change from baseline in LDL-C).

Another double-blind, placebo-controlled, 48-week trial (CHOICE I) enrolled 547 patients on maximally tolerated dose of statin who received Praluent 300 mg every 4 weeks (Q4W), 75 mg every 2 weeks (Q2W) or placebo, with criteria-based adjustment to 150 mg Q2W in the Praluent arms at week 12. The co-primary efficacy endpoints were evaluated at week 24 and from weeks 21 to 24 (mean percent change in LDL-C from baseline).

LONG TERM study

This multicentre, randomized, double-blind, placebo-controlled, 18-month study included 2341 patients (1553 patients in the alirocumab group and 788 patients in the placebo group) with HeFH or non-FH on a maximally tolerated dose of statin, with or without other lipid-modifying therapy. Patients received either alirocumab at a dose of 150 mg Q2W or placebo in addition to their existing lipid-modifying therapy.

The LONG TERM study included 17.7% HeFH patients and 68.6% non-FH patients with clinical atherosclerotic cardiovascular disease. The mean age was 60.5 years (range 18-89), 37.8% were women, 93% were Caucasian, 3% were Black, and 5% were Hispanic/Latino. The mean LDL-C at baseline was 3.15 mmol/L (122 mg/dL).

The proportion of patients who prematurely discontinued study drug prior to the 24-week endpoint was 8% among those treated with Praluent and 8% among those treated with placebo.

At week 24, the treatment difference between Praluent and placebo in mean LDL-C percent change was -58.5 % (95% CI:-61.1%, -55.8%; p-value: <0.0001) (see Table 8and Figure 3).

Table 8 – Mean Percent Change from Baseline and Difference[a] from Placebo in Lipid Parameters at Week 12 and Week 24 in the LONG TERM Study[b]

Treatment Group	LDL-C	Total-C	Non-HDL-C	Apo B
Week 12				
Placebo	1.3	0.1	0.8	0.4
Praluent (150 mg)	-61.4	-37.7	-52.3	-53.8
Difference from placebo (LS mean[c]) (95%CI)	-62.7 (-65.2, -60.3)	-37.8 (-39.4, -36.3)	-53.0 (-55.1, -50.9)	-54.2 (-56.6, -51.9)
p value[d]	<0.0001	<0.0001	<0.0001	<0.0001
Week 24				
Placebo	0.7	-0.3	0.6	1.1
Praluent (150 mg)	-57.8	-36.0	-49.1	-49.8
Difference from placebo (LS mean[c]) (95%CI)	-58.5 (-61.1, -55.8)	-35.7 (-37.4, -34.0)	-49.7 (-52.0, -47.4)	-50.9 (-53.3, -48.4)
p value[d]	<0.0001	<0.0001	<0.0001	<0.0001

Legend:
LDL-C: Low-density lipoprotein-cholesterol
Total-C: Total cholesterol
Non-HDL-C: Non-High-density lipoprotein cholesterol
Apo B: Apolipoprotein B-100

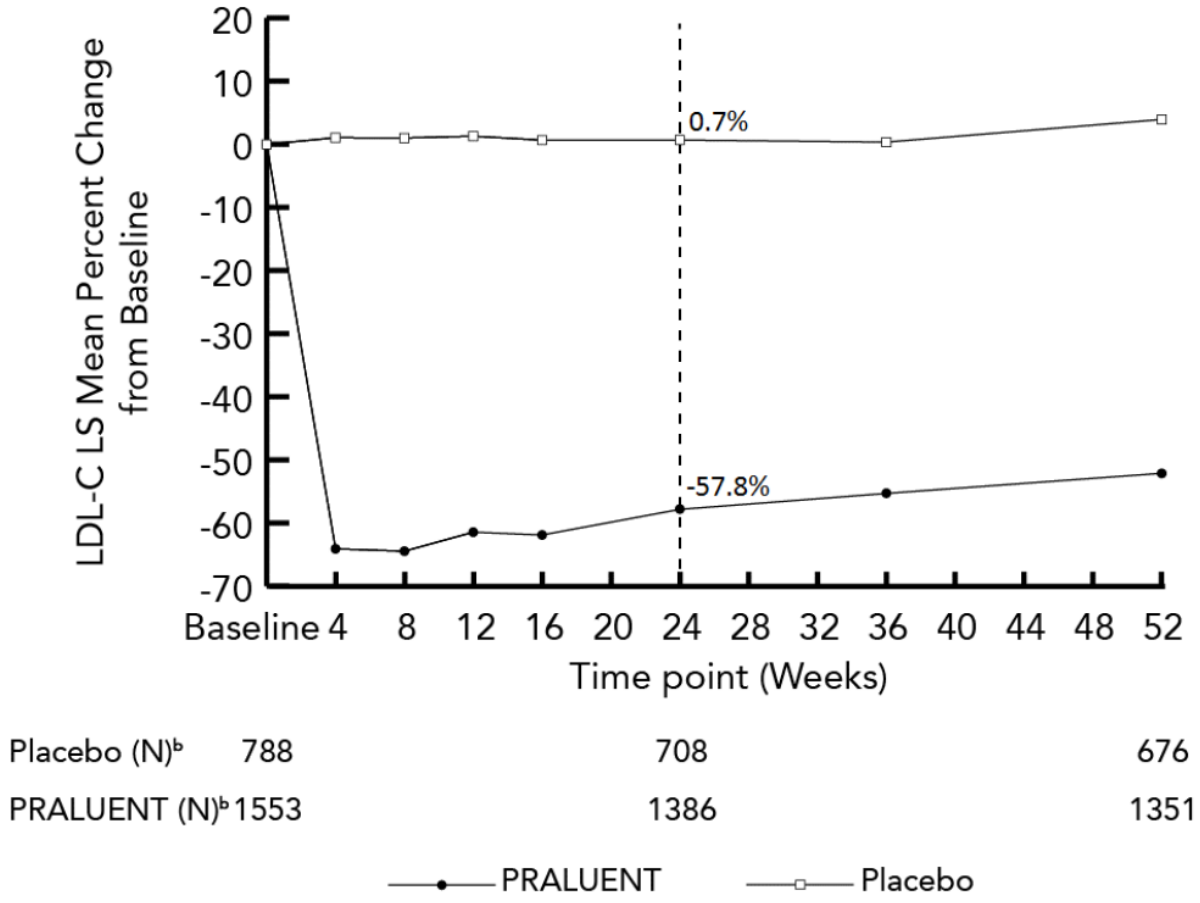
[a] Difference is Praluent minus placebo

[b] A pattern-mixture model approach was used with multiple imputation of missing post-treatment values based on a subject's own baseline value and multiple imputation of missing on-treatment values based on a model including available on-treatment values.

[c] Least-square (LS) means were obtained by combining LS means from analyses of covariance (ANCOVA) of the different imputed data sets, using Rubin's formulae. The ANCOVA models included the fixed categorical effect of treatment group and randomization strata, and the continuous fixed covariate of baseline value.

[d] A hierarchical testing procedure was used to test the primary and the key secondary efficacy endpoints while controlling for Type I error rate.

Figure 3 – Mean Percent Change from Baseline in LDL-C over 52 weeks in the LONG TERM study[a]



[a] The means were estimated based on all randomized patients, with multiple imputation of missing data taking into account treatment adherence

[b] Number of patients with observed data

COMBO I study

A multicentre, randomized, double-blind, placebo-controlled 52 week study included 316 patients (209 in the alirocumab group and 107 patients in the placebo group) categorized as very high CV risk with hypercholesterolemia on a maximally tolerated dose of statin, with or without other lipid-modifying therapy who required additional LDL-C reduction. Patients received either 75 mg alirocumab Q2W or placebo in addition to their existing lipid-modifying therapy. Dose up-titration of alirocumab to 150 mg Q2W occurred at week 12 in patients with LDL-C ≥1.81 mmol/L (70 mg/dL).

The mean age was 63 years (range 39-87), 34.2% were women, 82% were Caucasian, 16% were Black, and 11% were Hispanic/Latino. Overall 84% of patients had clinical atherosclerotic cardiovascular disease. The mean baseline LDL-C was 2.63 mmol/L (102 mg/dL).

The dose was up-titrated to 150 mg Q2W in 32 of 191 (16.8%) of patients treated beyond 12 weeks.

The proportion of patients who prematurely discontinued study drug prior to the 24-week endpoint was 11% among those treated with Praluent and 12% among those treated with placebo.

At week 24, the mean treatment difference from placebo in LDL-C percent change from baseline was -42.7% (95% CI: - 49.9%, - 35.4%; p-value: < 0.0001) (see Table 9).

Table 9 – Mean percent Change from Baseline and Difference[a] from Placebo in Lipid Parameters at Week 12 and Week 24 in the COMBO I Study[b]

Treatment Group	LDL-C	Total-C	Non-HDL-C	Apo B
Week 12				
Placebo	1.1	0.9	2.5	3.2
Praluent (75 mg)	-44.9	-24.7	-36.3	-33
Difference from placebo (LS mean[c]) (95%CI)	-46 (-52.6, -39.5)	-25.6 (-30.4, -20.7)	-38.8 (-45.2, -32.4)	-36.2 (-42.1, -30.2)
p value[d]	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Week 24				
Placebo	-1.5	-2.3	-1.1	0.2
Praluent (75/up to 150 mg)	-44.2	-25.6	-36.0	-33.6
Difference from placebo (LS mean[c]) (95%CI)	-42.7 (-49.9, -35.4)	-23.3 (-27.9, -18.7)	-34.8 (-41.3, -28.3)	-33.8 (-39.9, -27.7)
p value[d]	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Legend:
LDL-C: Low-density lipoprotein-cholesterol
Total-C: Total cholesterol
Non-HDL-C: Non-High-density lipoprotein cholesterol
Apo B: Apolipoprotein B-100

[a] Difference is Praluent minus placebo

[b] A pattern-mixture model approach was used with multiple imputation of missing post-treatment values based on a subject's own baseline value and multiple imputation of missing on-treatment values based on a model including available on-treatment values.

[c] Least-square (LS) means were obtained by combining LS means from analyses of covariance (ANCOVA) of the different imputed data sets, using Rubin's formulae. The ANCOVA models included the fixed categorical effect of treatment group and randomization strata, and the continuous fixed covariate of baseline value.

[d] A hierarchical testing procedure was used to test the primary and the key secondary efficacy endpoints while controlling for Type I error rate.

FH I and FH II studies

Two multicentre, placebo-controlled, double-blind 18-month studies included 735 patients (490 in the alirocumab group and 245 patients in the placebo group) with HeFH receiving a maximally tolerated dose of statin, with or without other lipid-modifying therapy. The trials were similar with regards to both design and eligibility criteria. Patients received either alirocumab 75 mg Q2W or placebo in addition to their existing lipid-modifying therapy. Dose up-titration of alirocumab to 150 mg Q2W occurred at week 12 in patients with LDL-C ≥ 1.81 mmol/L (70 mg/dL).

Overall, the mean age was 52 years (range 20-87), 45% were women, 94% were Caucasian, 1% were Black, and 3% were Hispanic/Latino. The proportion of patients in FH I study and in the FH II study with clinical atherosclerotic cardiovascular disease was 51.2% and 38.3% respectively. The mean baseline LDL-C was 3.74 mmol/L (144.6 mg/dL) in FH I study and 3.48 mmol/dL (134.4 mg/dL) in FH II study. The dose was up-titrated beyond week 12 in 135 of 311 patients (43.4%) in FHI study and in 61 of 158 patients (38.6%) in FH II study.

The proportion of patients who prematurely discontinued study drug prior to the 24-week endpoint was 6.5% among those treated with Praluent and 5.5% among those treated with placebo in the FH I study and 4.8% among those treated with Praluent and 2.4% among those treated with placebo in the FH II study.

At week 24, the mean treatment difference from placebo in LDL-C percent change from baseline in FH I study was -56.3% (95% CI: -61.8%, -50.7%; p-value: < 0.0001) (see Table 10 and Figure 4). At week 24, the mean treatment difference from placebo in LDL-C percent change from baseline in FH II study was -50.2% (95% CI:-57.1%, -43.2%; p-value: < 0.0001) (see Table 10 and Figure 5).

Table 10 – Mean Percent Change from Baseline and Difference[a] from Placebo in Lipid Parameters at Week 12 and Week 24 in Studies FH I[b] and FH II[b]

Treatment Group	FH I				FH II			
	LDL-C	Total-C	Non-HDL-C	Apo B	LDL-C	Total-C	Non-HDL-C	Apo B
Week 12								
Placebo	5.6	4.1	5.2	3.2	4.6	3.4	4.1	-0.7
Praluent (75 mg)	-42.8	-27.9	-37.8	-33.7	-43.1	-26.2	-37.3	-34.7
Difference from placebo (LS mean[c]) (95%CI)	-48.4 (-53.3, -43.5)	-32.0 (-35.3, -28.6)	-43.0 (-47.3, -38.6)	-36.9 (-40.7, -33.0)	-47.6 (-54.1, -41.2)	-29.5 (-34.2, -24.9)	-41.4 (-47.3, -35.5)	-34.0 (-38.9, -39.1)
p value[d]	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Week 24								
Placebo	9.0	7.1	9.5	4.8	2.8	2.1	3.0	-3.4
Praluent (75mg/up to 150 mg)	-47.2	-30.5	-41.5	-39.2	-47.3	-29.9	-41.5	-41.4
Difference from placebo (LS mean[c]) (95%CI)	-56.3 (-61.8, -50.7)	-37.7 (-41.5, -33.8)	-51.0 (-56.0, -46.0)	-44 (-48.3, -39.7)	-50.2 (-57.1, -43.2)	-31.9 (-36.7, -27.1)	-44.6 (-50.8, -38.4)	-37.9 (-43.0, -32.8)
p value[d]	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Legend:
LDL-C: Low-density lipoprotein-cholesterol
Total-C: Total cholesterol
Non-HDL-C: Non-High-density lipoprotein cholesterol
Apo B: Apolipoprotein B-100

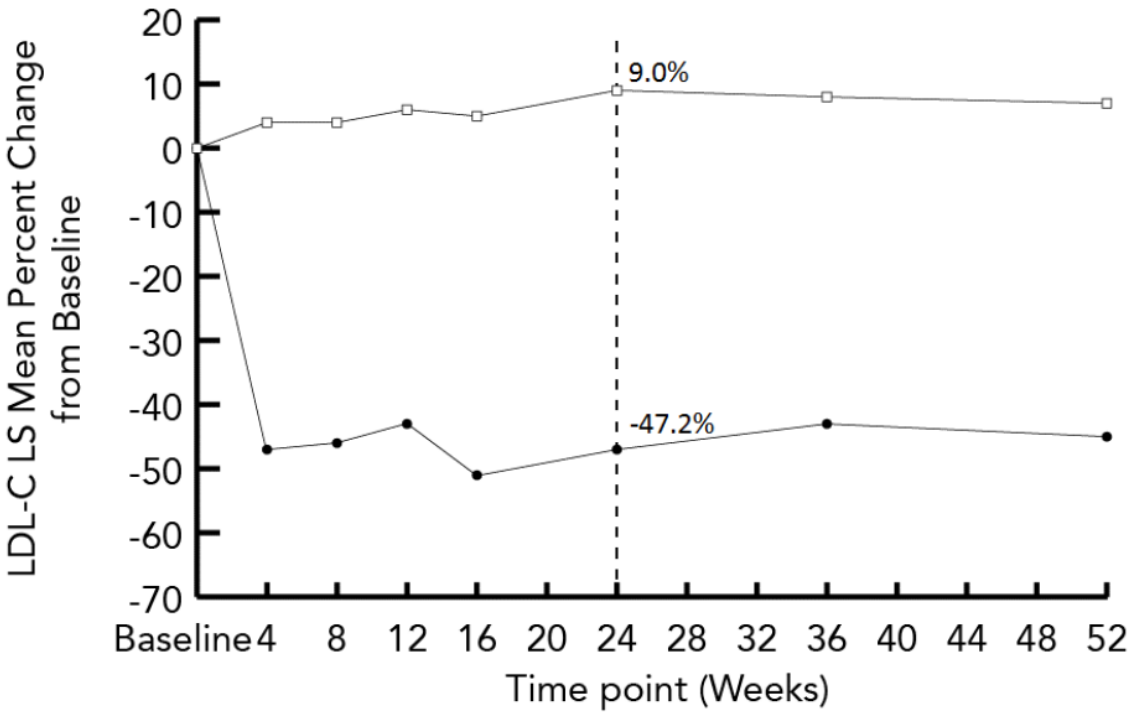
[a] Difference is Praluent minus placebo

[b] A pattern-mixture model approach was used with multiple imputation of missing post-treatment values based on a subject's own baseline value and multiple imputation of missing on-treatment values based on a model including available on-treatment values.

[c] Least-square (LS) means were obtained by combining LS means from analyses of covariance (ANCOVA) of the different imputed data sets, using Rubin's formulae. The ANCOVA models included the fixed categorical effect of treatment group and randomization strata, and the continuous fixed covariate of baseline value.

[d] A hierarchical testing procedure was used to test the primary and the key secondary efficacy endpoints while controlling for Type I error rate.

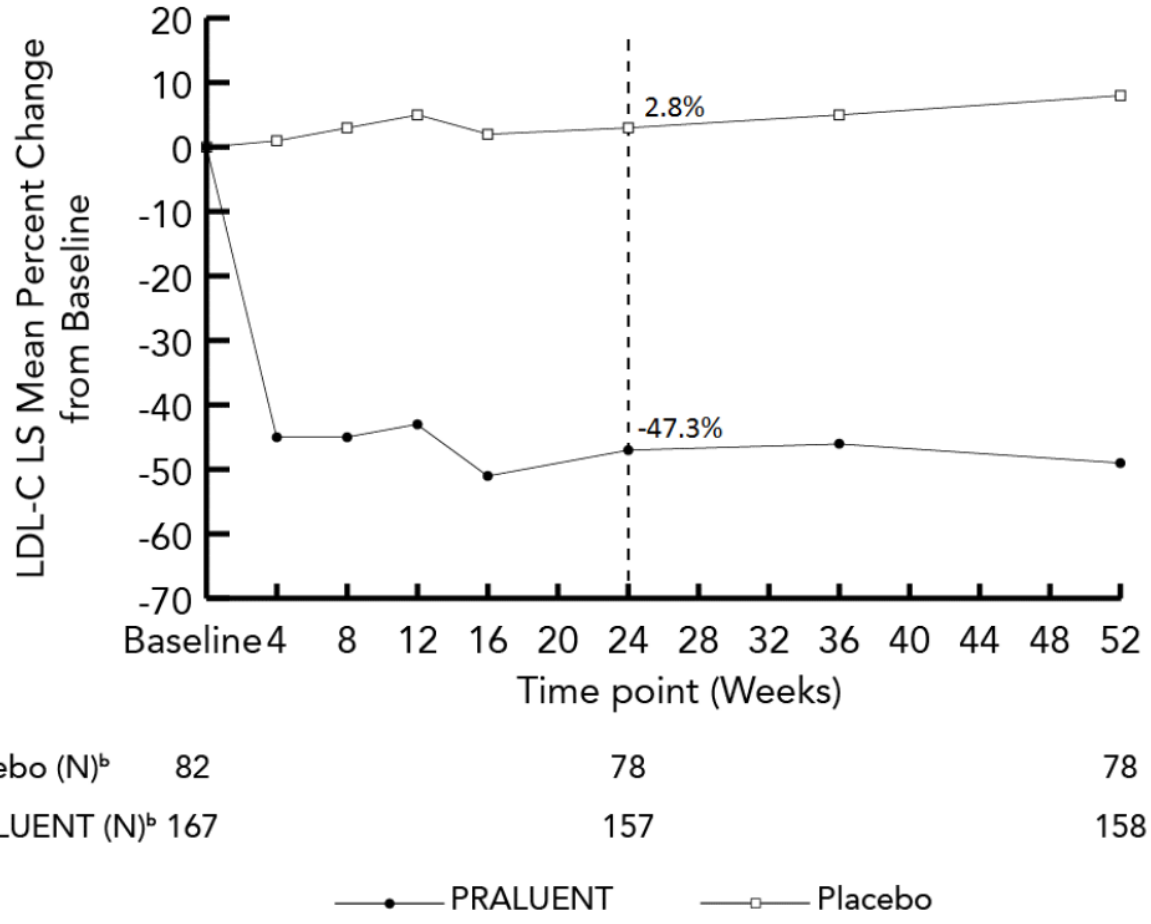
Figure 4 – Mean Percent Change from Baseline in LDL-C over 52 weeks in FH I Study[a]



[a] The means were estimated based on all randomized patients, with multiple imputation of missing data taking into account treatment adherence

[b] Number of patients with observed data

Figure 5 – Mean Percent Change from Baseline in LDL-C over 52 weeks in FH II Study[a]



[a] The means were estimated based on all randomized patients, with multiple imputation of missing data taking into account treatment adherence

[b] Number of patients with observed data

HIGH FH study

HIGH FH was a multicentre, randomized, double-blind, placebo-controlled 18-month study that included 107 HeFH patients (72 patients in the alirocumab group and 35 patients in the placebo group) on a maximally tolerated dose of statin, with or without other lipid-modifying therapies, and a baseline LDL-C ≥ 4.14 mmol/L (160 mg/dL). Patients received either alirocumab at a dose of 150 mg Q2W or placebo in addition to their existing lipid-modifying therapy.

The mean age was 50.6 years (range 18-80), 46.7% were women, 88% were Caucasian, 2% were Black, and 6% were Hispanic/Latino. Overall, 50% of patients had clinical atherosclerotic cardiovascular disease. Mean baseline LDL-C was 5.08 mmol/L (196.3 mg/dL) in the alirocumab group and 5.2 mmol/L (201.0 mg/dL) in the placebo group.

The proportion of patients who discontinued study drug prior to the 24-week endpoint was 10% among those treated with Praluent and 0% among those treated with placebo.
At week 24, the mean treatment difference from placebo in LDL-C percent change from baseline was -36.3% (95% CI: -48.5%, -24.2%; p-value: < 0.0001) (see Table 11).

Table 11 – Mean percent Change from Baseline and Difference[a] from Placebo in Lipid Parameters at Week 12 and Week 24 in the HIGH FH Study[b]

Treatment Group	LDL-C	Total-C	Non-HDL-C	Apo B
Week 12				
Placebo	-6.7	-5.1	-7.0	-9.1
Praluent (150 mg)	-46.9	-33.2	-41.8	-39.3
Difference from placebo (LS mean[c]) (95%CI)	-40.3 (-51.3, -29.2)	-28.1 (-36.3, -19.8)	-34.8 (-45.0, -24.6)	-30.2 (-39.2, -21.3)
p value[d]	<0.0001	<0.0001	<0.0001	<0.0001
Week 24				
Placebo	-6.9	-4.8	-6.2	-8.6
Praluent (150 mg)	-43.3	-31.3	-39.7	-36.5
Difference from placebo (LS mean[c]) (95%CI)	-36.3 (-48.5, -24.2)	-26.5 (-35.5, -17.4)	-33.5 (-44.2, -22.7)	-28.0 (-37.6, -18.3)
p value[d]	<0.0001	<0.0001	<0.0001	<0.0001

Legend:
LDL-C: Low-density lipoprotein-cholesterol
Total-C: Total cholesterol
Non-HDL-C: Non-High-density lipoprotein cholesterol
Apo B: Apolipoprotein B-100
[a] Difference is Praluent minus placebo
[b] A pattern-mixture model approach was used with multiple imputation of missing post-treatment values based on a subject's own baseline value and multiple imputation of missing on-treatment values based on a model including available on-treatment values.
[c] Least-square (LS) means were obtained by combining LS means from analyses of covariance (ANCOVA) of the different imputed data sets, using Rubin's formulae. The ANCOVA models included the fixed categorical effect of treatment group and randomization strata, and the continuous fixed covariate of baseline value.

[d] A hierarchical testing procedure was used to test the primary and the key secondary efficacy endpoints while controlling for Type I error rate.

CHOICE I

CHOICE I was a double-blind, placebo-controlled 48-week trial that randomly assigned 458 patients to Praluent 300 mg every 4 week dosing regimen (Q4W), 115 patients to Praluent 75 mg every 2 weeks (Q2W), and 230 patients to placebo. All 803 patients had hypercholesterolemia and were receiving concomitant statins (68.1%) or other lipid modifying therapy (39.8%). The primary efficacy endpoint was measured at week 24 (mean percent change in LDL-C from baseline). At week 12, if additional LDL-C lowering was required based on pre-specified LDL-C criteria, Praluent was adjusted to 150 mg Q2W in the Praluent treatment groups for the remainder of the trial. Approximately 20% of patients treated with Praluent 75 mg Q2W or 300 mg Q4W for at least 12 weeks required dose adjustment to 150 mg Q2W.

The mean age was 61years (range 21-88), 42 % were women, 87% were Caucasian, 11% were Black, and 3% were Hispanic/Latino. Overall, 64% of patients had atherosclerotic cardiovascular disease; 27% of patients had type 2 diabetes at baseline. The proportion of patients who discontinued study drug prior to the 24-week endpoint was 12% among those treated with Praluent 300 mg Q4W, 14% among those treated with Praluent 75 mg Q2W and 15% among those treated with placebo.

In the cohort of patients on background statin, the mean LDL-C at baseline was 2.92 mmol/L.

At week 24, the treatment difference between initial assignment to Praluent 300 mg Q4W and placebo in mean percent change from baseline in LDL-C was -56% (97.5% CI: -62%, -49%; p-value: <0.0001), and the treatment difference between initial assignment to Praluent 75 mg Q2W and placebo in mean percent change in LDL-C from baseline was -48% (97.5% CI: -57%, -39%).

In the cohort of patients not treated with a concomitant statin, the mean LDL-C at baseline was 3.67 mmol/L (142 mg/dL).

At week 24, the treatment difference between initial assignment to Praluent 300 mg Q4W and placebo in mean percent change in LDL-C from baseline was - 48% (97.5% CI: -56%, -39%; p-value: <0.0001), and the treatment difference between initial assignment to Praluent 75 mg Q2W and placebo in mean percent change in LDL-C from baseline was -45% (97.5% CI: -57%, -34%; p-value: <0.0001).

In the subgroup of patients with pre-existing type II diabetes mellitus, percent reduction in LDL-C was consistent with the overall population.

Neurocognitive Function (R727-CL-1532)

A 96 week, randomized, double-blind, placebo-controlled trial evaluated the effect of PRALUENT on neurocognitive endpoints after 96 weeks of treatment (1.8 years) in patients aged 40 to 85 years old with heterozygous familial hypercholesterolemia (HeFH) or non-familial hypercholesterolemia, at high or very high cardiovascular risk, who did not have cognitive impairment or dementia. Nearly all patients (> 91.3%) were taking background lipid-modifying therapy (LMT) consisting of a maximally tolerated dose of statin, with or without other LMTs.

Neurocognitive function was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB). A total of 2171 patients were randomized; 1087 patients were treated with alirocumab 75 mg and/or 150 mg every 2 weeks and 1084 patients were treated with placebo. A majority (>80%) of patients in each group completed the 96-week, double-blind treatment period.

After 96 weeks of treatment, PRALUENT was non-inferior to placebo on select cognitive function domains. The percentage of patients who reported neurocognitive disorders was 1.3% in the PRALUENT treatment group and 1.7% in the placebo group.

COMBO II study

COMBO II study was a multicentre, randomized, double-blind, ezetimibe-controlled 2 year study that included 720 patients (479 patients in the alirocumab group and 241 patients in the ezetimibe group) categorized as very high CV risk with hypercholesterolemia, on a maximally tolerated dose of statin. Patients received either alirocumab 75 mg Q2W or ezetimibe 10 mg once daily in addition to their existing statin therapy. Dose up-titration of alirocumab to 150 mg Q2W occurred at week 12 in patients with LDL-C ≥ 1.81 mmol/L (70 mg/dL); the dose was up-titrated to 150 mg Q2W in 82 (18%) of 446 patients treated with PRALUENT for at least 12 weeks.

The mean age was 61.6 years (range 29-88), 26.4% were women, 84.7% were Caucasian, 3.9% were Black, and 2.8% were Hispanic/Latino. Overall 90.1% of patients had clinical atherosclerotic cardiovascular disease; 30.7% of patients had type 2 diabetes at baseline. Mean baseline LDL-C was 2.81 mmol/L (108.6 mg/dL) in the alirocumab group and 2.7 mmol/L (104.6 mg/dL) in the ezetimibe group. The dose was up-titrated to 150 mg Q2W in 82 of 446 (18.4%) of patients treated beyond 12 weeks.

The proportion of patients who prematurely discontinued study drug prior to the 24-week endpoint was 8.6% among those treated with PRALUENT and 9.5% among those treated with ezetimibe.

At week 24, the mean percent change from baseline in LDL-C was -47.8% with PRALUENT and -20.1% with ezetimibe, and the mean treatment difference from ezetimibe in LDL-C percent change from baseline was - 27.7% (95% CI: -32.5%, -22.9%, ; p-value: < 0.0001).

In the subgroup of patients with pre-existing type II diabetes mellitus, percent reduction in LDL-C was consistent with the overall population.

ALTERNATIVE study

ALTERNATIVE study was a multicentre, double-blind, ezetimibe-controlled trial in patients for whom the maximally tolerated daily dose of statin was contraindicated due to skeletal muscle-related symptoms, with 126 patients randomly assigned to Praluent 75 mg Q2W/150 mg Q2W and 125 patients to ezetimibe 10 mg/day. At week 12, if additional LDL-C lowering was required based on pre-specified LDL-C criteria, Praluent was up-titrated to 150 mg Q2W for the remainder of the trial. The dose was up-titrated to 150 mg Q2W in 54 (50%) of 109 patients treated with Praluent for at least 12 weeks.

There were 48.7% of patients that were on concomitant non-statin lipid modifying therapy other than ezetimibe. The mean age was 63 years (range 31-88), 45% were women, 94% were Caucasian, 4% were Black, and 2% were Hispanic/Latino; 23.9% of patients had type 2 diabetes at baseline. Mean baseline LDL-C was 4.9 mmol/L (191 mg/dL).

The proportion of patients who prematurely discontinued study drug prior to the 24-week endpoint was 24% among those treated with Praluent and 33% among those treated with ezetimibe.

At week 24, the mean percent change from baseline in LDL-C was -44% with Praluent and -13% with ezetimibe, and the treatment difference between Praluent and ezetimibe in mean LDL-C percent change was -30% (95% CI: -37%, -24%; p-value: <0.0001).

In the subgroup of patients with pre-existing type II diabetes mellitus, percent reduction in LDL-C was consistent with the overall population.

MONO study
MONO study was a multicentre, double-blind, ezetimibe-controlled trial in patients with a moderate CV risk, not taking statins or other lipid-modifying therapies, and a baseline LDL-C between 2.59-4.9 mmol/L (100 mg/dL to 190 mg/dL) that randomly assigned 52 patients to Praluent 75 mg Q2W and 51 patients to ezetimibe 10 mg/day. At week 12, if additional LDL-C lowering was required based on pre-specified LDL-C criteria, Praluent was up-titrated to 150 mg Q2W for the remainder of the trial. The dose was up-titrated to 150 mg Q2W in 14 (30%) of 46 patients treated with Praluent for at least 12 weeks.

The mean age was 61 years (range 49-72), 46% were women, 89% were Caucasian and 12% were Black. Mean baseline LDL-C was 141 mg/dL. The proportion of patients who prematurely discontinued study drug prior to the 24-week endpoint was 15% among those treated with Praluent and 14% among those treated with ezetimibe.

At week 24, the mean percent change from baseline in LDL-C was -45% with Praluent and -14% with ezetimibe, and the treatment difference between Praluent and ezetimibe in mean LDL-C percent change was -31% (95% CI: -40%, -22%; p-value: <0.0001).

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

No significant adverse effects were observed in rats and cynomolgus monkeys when administered alirocumab by subcutaneous or intravenous injection up to dose levels of 75 mg/kg QW for 6 months.

There were no additive or synergistic adverse effects when alirocumab was administered in combination with atorvastatin to cynomolgus monkeys up to dose levels of 75/mg/kg QW and 40 mg/kg QD, respectively, for 3 months.

Carcinogenicity, mutagenicity and genotoxicity studies have not been conducted with alirocumab. There were no adverse effects on surrogate markers of fertility (e.g. estrous cyclicity, testicular volume or sperm parameters) up to doses of 75 mg/kg QW included in a 26-week chronic subcutaneous toxicology study in sexually-mature monkeys. In addition, there were no alirocumab-related anatomic pathology or histopathology findings in reproductive tissues in any rat or monkey toxicology study.

No effects on embryo-fetal development were observed in Sprague Dawley rats up to doses of 75 mg/kg by subcutaneous route on gestational day 6 and 12. Studies in monkeys showed that alirocumab crosses the placental barrier and is pharmacologically active in infants exposed during organogenesis through parturition. Dose-related decreases in T-cell dependent antibody response

(TDAR) to keyhole limpet hemocyanin (KLH) were observed at doses ≥ 15 mg/kg QW in offspring of exposed mothers at 4 to 6 months of age, suggesting a suppression of humoral immune response. Recovery of infant immune function was not assessed. Studies in monkeys did not demonstrate any additional embryo-fetal, pre- or postnatal or maternal effects up to doses of 75 mg/kg QW.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrPRALUENT®

alirocumab injection

solution for subcutaneous injection

75 mg, 150 mg, and 300 mg

Read this carefully before you start taking **Praluent** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Praluent**.

What is Praluent used for?

Praluent is used:

- To reduce the risk of heart attack, stroke, and certain types of heart procedures (to restore blood flow to the heart) in adults with cardiovascular disease.
- To reduce low density lipoprotein cholesterol (LDL-C) levels in adults with high cholesterol levels (hypercholesterolemia, heterozygous familial and non-familial).

Praluent can be used along with lifestyle changes, by itself or with other medicines (such as statins or ezetimibe) to treat patients with high cholesterol. Continue to follow your cholesterol-lowering diet while taking this medicine.

It is not known if Praluent is safe and effective in children.

How does Praluent work?

Praluent is an injectable medicine that belongs to a type of medicines called PCSK9 inhibitors.

- Praluent is a fully human monoclonal antibody that blocks a protein called PCSK9 (proprotein convertase subtilisin kexin type 9).
- PCSK9 is a protein secreted by liver cells.
- LDL (“bad”) cholesterol is normally removed from the blood by binding to specific receptors (docking stations) on liver cells. PCSK9 lowers the number of LDL receptors available to remove LDL cholesterol from the blood.
- Praluent blocks PCSK9 and thereby increases the number of receptors available to remove LDL cholesterol from the blood. This results in lower LDL cholesterol levels.

What are the ingredients in Praluent?

Medicinal ingredients: alirocumab

Non-medicinal ingredients: histidine, polysorbate 20, sucrose and water for injection

Praluent comes in the following dosage form:

- Pre-filled pen

Do not use Praluent if:

- you are allergic to alirocumab or to any of the other ingredients in this medicine

To help avoid side effects and ensure proper use of Praluent, talk to your healthcare professional about any health conditions or problems you may have before taking this medicine, including if you:

- have allergies. If you have a serious allergic reaction, stop using Praluent and tell your doctor or pharmacist.
- are pregnant or intend to get pregnant. Tell your doctor or pharmacist before using this medicine. The use of Praluent is not recommended during pregnancy.
- are breastfeeding or plan to breastfeed. Tell your doctor or pharmacist before using this medicine. The use of Praluent is not recommended during breast-feeding.

Other warnings you should know about:
The safety and efficacy have not been established in children and adolescents less than 18 years of age. Therefore, the use of Praluent is not recommended in this age group.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take Praluent:
Praluent is injected under the skin (subcutaneous use) of your upper leg (thigh), stomach area (abdomen), or upper arm.

Always check the label of your pre-filled pen to make sure you have the correct product and the correct strength of Praluent before each injection.

To allow the solution to come to room temperature, remove the 75 mg or 150 mg pen from the refrigerator approximately 30 to 40 min before the injection, or the 300 mg pen approximately 45 minutes before the injection.

Choose a different spot each time you inject (e.g. right thigh then left thigh, or right abdomen then left abdomen).

Do not inject into areas where the skin is injured, tender, hard, red or hot.

Do not inject Praluent together with other injectable medicines at the same injection site.

Praluent comes as a single-dose (1 time) pre-filled pen (autoinjector). Your healthcare provider will prescribe the dose that is best for you.

Before starting Praluent, you should be on a diet to lower your cholesterol. You should stay on this cholesterol lowering diet while taking Praluent.

If your doctor has prescribed Praluent along with a statin or other cholesterol lowering medicine, follow your doctor's instructions on how to take these medicines together. In this case, please read the dosage instructions in the package leaflet of the other medicines.

Ask your doctor if you have any further questions on how to use Praluent.

Learning how to use the pre-filled pen
Before you use the pre-filled pen for the first time, your doctor, pharmacist or nurse will show you how to inject Praluent.

- Always read the "Instructions for Use" provided in the box.
- Always use the pre-filled pen as described in the “Instructions for Use”.

Usual dose:
Praluent is available as 75 mg, 150 mg, or 300 mg for subcutaneous administration. Your doctor will tell you which dosage (75 mg or 150 mg every 2 weeks or 300 mg every 4 weeks) is right for you.

To give the 300 mg dose, give either one 300 mg injection, or two 150 mg injections in a row at two different injection sites.

Do not stop using Praluent without talking with your doctor. If you stop using Praluent, your cholesterol levels can increase.

Overdose:

If you think you have taken too much Praluent, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of Praluent, inject your missed dose as soon as you are able to do so, within 7 days. Then take your next dose at your regular scheduled time:

- If you take Praluent every 2 weeks, take your next dose 2 weeks from the day you missed your dose.
- If you take Praluent every 4 weeks, take your next dose 4 weeks from the day you missed your dose.

If you miss a dose by more than 7 days:

- If you take Praluent every 2 weeks, wait until your next dose scheduled to re-start.
- If you take Praluent every 4 weeks, start a new schedule from the time you remember to take your dose.

In case you are not sure when to inject Praluent, call your doctor, nurse or pharmacist.

What are possible side effects from using Praluent?
Praluent may cause allergic reactions that can be severe and require treatment in a hospital. Call your healthcare provider or go to the nearest hospital emergency room right away if you have any symptoms of an allergic reaction, including a severe rash, redness, severe itching, swelling of the face, lips, throat or tongue, or trouble breathing.

These are not all the possible side effects you may feel when taking Praluent. If you experience any side effects not listed here, contact your healthcare professional. Please also see “Do not use Praluent if” and “Other warnings you should know about”.

Common (may affect up to 1 in 10 people)

- Redness, swelling, pain, tenderness, or bruising (hematoma) where the injection is given (local injection site reactions)
- Symptoms of the common cold
- Itching (pruritus)

Rare (may affect up to 1 in 1,000 people):

- Allergic reactions
- Hypersensitivity vasculitis: a specific form of allergic reaction, with symptoms such as rash or purple-coloured spots on the skin, diarrhea.
- Hives (urticaria)
- Reddish skin spots, sometimes with blisters (nummular eczema)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE (may affect up to 1 in 1,000 people)			
Allergic reactions			✓
Hypersensitivity vasculitis, which is a specific form of allergic reaction. Symptoms may include diarrhea, rash, or purple-coloured spots on the skin (purpura)			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-healthproducts/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Keep out of reach and sight of children.

Do not use this medicine after the expiry date which is stated on the label and carton.

Store in a refrigerator (2°C - 8°C). Do not freeze.

Keep the pen in the outer carton in order to protect from light.

Do not expose to extreme heat.

Praluent should be allowed to warm to room temperature prior to use. Praluent should be used as soon as possible after it has warmed up. When taken out of the refrigerator to warm up the pen, do not put near a heat source or in direct sunlight. Do not keep Praluent for more than 30 days at room temperature.

Do not use this medicine if the solution is discoloured or cloudy, or if it contains visible flakes or particles.

After use, put the pen into a puncture-resistant container. Always keep the container out of the reach of children. Ask your health care provider or pharmacist how to throw away the container. Do not recycle the container.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

If you want more information about Praluent:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website: www.sanofi.com/en/canada, or by calling 1-800-265-7927.

This leaflet was prepared by Sanofi-aventis Canada Inc.

Last revised:

INSTRUCTIONS FOR USE

Praluent (alirocumab) 75 mg solution for injection in a pre-filled pen

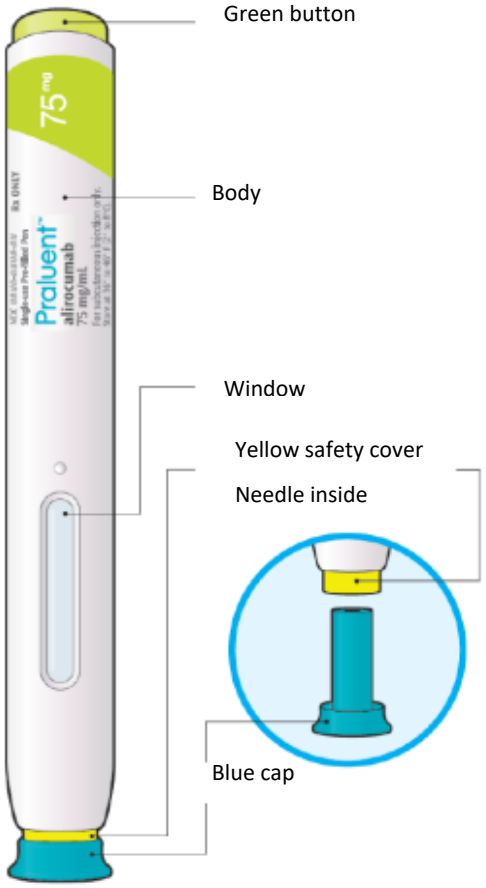
IMPORTANT INFORMATION

- The device is a single use disposable pen. It contains 75 mg of Praluent (alirocumab) in 1 mL.
- The Praluent pen contains medicine prescribed by your doctor.
- The medicine is injected under your skin and can be given by yourself or someone else (caregiver).
- This pen can only be used for one single injection, and must be discarded after use.

Do	Do not
• Keep the Praluent pen out of the reach of children. • Read all of the instructions carefully before using the Praluent pen. • Follow these instructions every time you use a Praluent pen. • Store unused pens in the refrigerator at 36°F to 46°F (2°C to 8°C). For detailed storage conditions see separate Patient Medication Information leaflet for Praluent.	• Do not touch the yellow safety cover. • Do not use the pen if it has been dropped or damaged. • Do not use the pen if the blue cap is missing or not securely attached. • Do not re-use a pen. • Do not shake the pen. • Do not freeze the pen. • Do not expose the pen to extreme heat. • Do not expose the pen to direct sunlight.

Keep this leaflet. If you have questions, ask your doctor, pharmacist or nurse or call the sanofi-aventis number on the patient leaflet.

The parts of the Praluent pen are shown in this picture.



For single use only

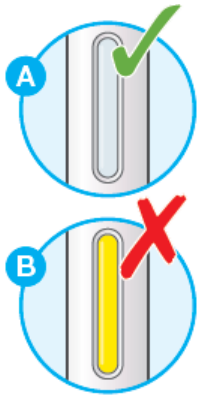
STEP A: GETTING READY FOR AN INJECTION

Before you start you will need:

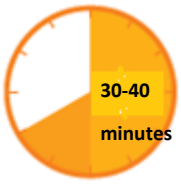
- the Praluent pen,
- alcohol wipes,
- cotton ball or gauze,
- a puncture-resistant container (see STEP B-8).

1. **Look at the label on the pen.**
   - Check that you have the correct product and the correct dose.
   - Check the use by date: do not use if this date has passed.

2. **Look at the window.**
   - Check the liquid is clear, colourless to pale yellow and free from particles - if not, do not use (see picture A).
   - You may see an air bubble. This is normal.
   - Do not use if the window appears solid yellow (see picture B).
   - Do not use this medicine if the solution is discoloured or cloudy, or if it contains visible flakes or particles.



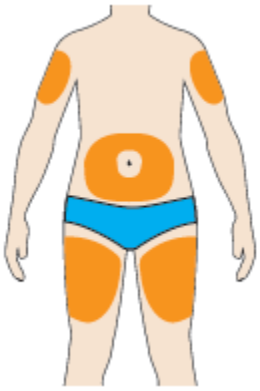
3. **Let the pen warm up at room temperature for 30 to 40 minutes.**
   - This is important for administering the entire dose and helps minimize discomfort.
   - Take Praluent out of the refrigerator to warm up before using.
   - Do not heat the pen; let it warm up on its own.
   - Use the pen as soon as possible after it has warmed up.
   - Do not put the pen back in the refrigerator.



4. **Prepare the injection site.**
    - Wash your hands with soap and water and dry with a towel.
    - Clean skin in the injection area with an alcohol wipe.
    - You can inject into your (see below picture):
        - thigh
        - belly (except for the 5 cm/2 inch area around your navel)
        - upper arm
    - You can stand or sit to give yourself an injection.

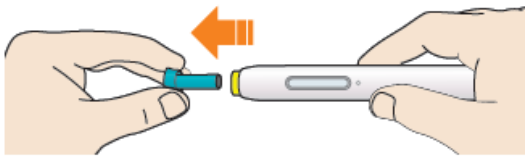
    Important:

    - Change (rotate) your injection site each time you give yourself an injection. If you need to use the same injection area, make sure it is not the same spot on the site you used last time.
    - Do not inject into areas where the skin is injured, tender, hard, red, or hot. Do not inject Praluent into areas with visible veins, scars or stretch marks



STEP B: HOW TO INJECT

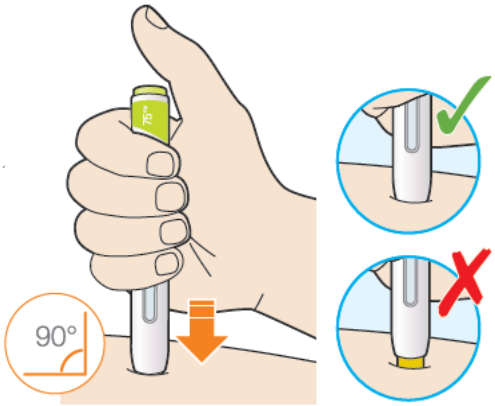
1. **After completing all steps in "STEP A: GETTING READY FOR AN INJECTION", pull off the blue cap**
    - Do not pull off the cap until you are ready to inject.
    - Do not put the blue cap back on.



2. **Hold the Praluent pen like this.**

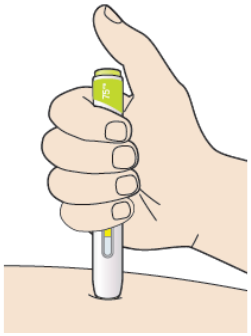
- Do not touch the yellow safety cover.
- Make sure you can see the window.

3. **Press the yellow safety cover on your skin at roughly a 90° angle.**
    - Press and firmly hold the pen against your body until the yellow safety cover is no longer visible. The pen will not work if the yellow safety cover is not depressed fully.
    - If needed, pinch the skin to make sure the injection site is firm.



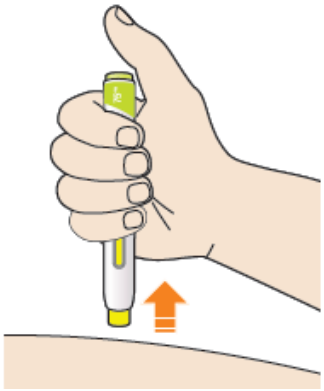
4. **Push and immediately release the green button with your thumb.**
    - You will hear a click. Your injection has now started.
    - The window will start to turn yellow.

5. **Keep holding the pen against your skin after releasing the button**
   - The injection may take up to 20 seconds.



6. **Check the window has turned yellow, before removing the pen.**
   - Do not remove the pen until the entire window has turned yellow.
   - Your injection is complete, when the window has turned completely yellow, you may hear a second click.
   - If the window does not turn completely yellow, call 1-800-265-7927 for help. Do not give yourself a second dose without speaking to your doctor, pharmacist or nurse.

7. **Pull pen away from your skin.**
   - Do not rub the skin after the injection.
   - If you see any blood, press a cotton ball or gauze on the site until the bleeding stops.



8. Discard pen and cap

- Do not put the blue cap back on.
- Throw away the pen in a puncture-resistant container immediately after they have been used
- Dispose of used container according to your local regulations.
- Always keep the container out of the reach of children.

Praluent (alirocumab) 150 mg solution for injection in a pre-filled pen

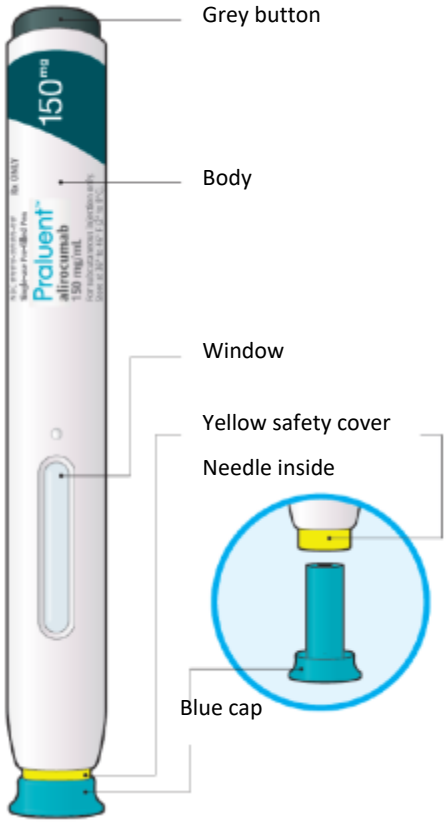
IMPORTANT INFORMATION

- The device is a single use disposable pen. It contains 150 mg of Praluent (alirocumab) in 1 mL.
- The Praluent pen contains medicine prescribed by your doctor.
- The medicine is injected under your skin and can be given by yourself or someone else (caregiver).
- This pen can only be used for one single injection, and must be discarded after use.

Do	Do not
• Keep the Praluent pen out of the reach of children. • Read all of the instructions carefully before using the Praluent pen. • Follow these instructions every time you use a Praluent pen. • Store unused pens in the refrigerator at 36°F to 46°F (2°C to 8°C). For detailed storage conditions see separate Patient Medications Information leaflet for Praluent.	• Do not touch the yellow safety cover. • Do not use the pen if it has been dropped or damaged. • Do not use the pen if the blue cap is missing or not securely attached. • Do not re-use a pen. • Do not shake the pen. • Do not freeze the pen. • Do not expose the pen to extreme heat. • Do not expose the pen to direct sunlight.

Keep this leaflet. If you have questions, ask your doctor, pharmacist or nurse or call the sanofi-aventis number on the patient leaflet.

The parts of the Praluent pen are shown in this picture.



For single use only

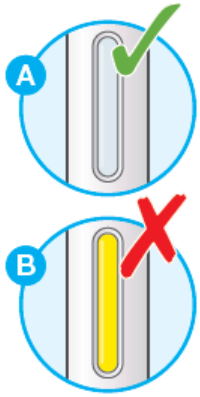
STEP A: GETTING READY FOR AN INJECTION

Before you start you will need:

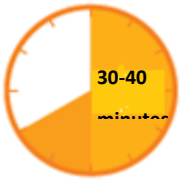
- the Praluent pen,
- alcohol wipes,
- cotton ball or gauze,
- a puncture-resistant container (see STEP B-8).

1. **Look at the label on the pen.**
   - Check that you have the correct product and the correct dose.
   - Check the use by date: do not use if this date has passed.

2. **Look at the window.**
   - Check the liquid is clear, colourless to pale yellow and free from particles - if not, do not use (see picture A).
   - You may see an air bubble. This is normal.
   - Do not use if the window appears solid yellow (see picture B).
   - Do not use this medicine if the solution is discoloured or cloudy, or if it contains visible flakes or particles.



3. **Let the pen warm up at room temperature for 30 to 40 minutes.**
   - This is important for administering the entire dose and helps minimize discomfort.
   - Take Praluent out of the refrigerator to warm up before using.
   - Do not heat the pen, let it warm up on its own.
   - Use the pen as soon as possible after it has warmed up.
   - Do not put the pen back in the refrigerator.



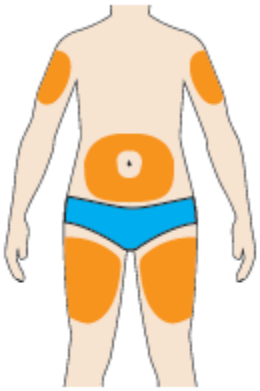
4. **Prepare the injection site.**
   - Wash your hands with soap and water and dry with a towel.
   - Clean skin in the injection area with an alcohol wipe.
   - You can inject into your (see below picture):

- thigh
- belly (except for the 5 cm/2 inch area around your navel)
- upper arm

- You can stand or sit to give yourself an injection.

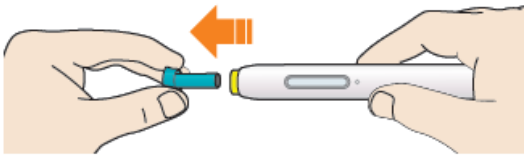
Important:

- Change (rotate) your injection site each time you give yourself an injection. If you need to use the same injection area, make sure it is not the same spot on the site you used last time.
- Do not inject into areas where the skin is injured, tender, hard, red, or hot. Do not inject Praluent into areas with visible veins, scars or stretch marks.



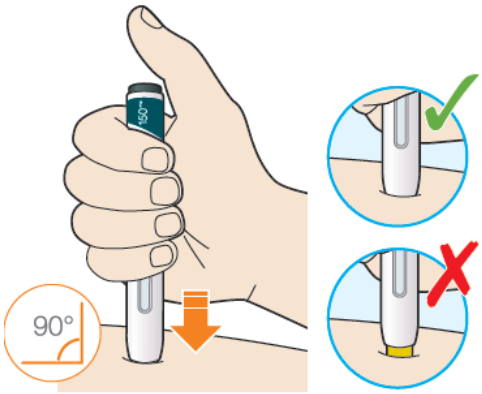
STEP B: HOW TO INJECT

1. **After completing all steps in "STEP A: GETTING READY FOR AN INJECTION", pull off the blue cap**
   - Do not pull off the cap until you are ready to inject.
   - Do not put the blue cap back on.



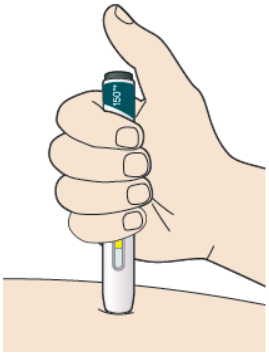
2. **Hold the Praluent pen like this.**
   - Do not touch the yellow safety cover.
   - Make sure you can see the window.

3. **Press the yellow safety cover on your skin at roughly a 90° angle.**
   - Press and firmly hold the pen against your body until the yellow safety cover is no longer visible. The pen will not work if the yellow safety cover is not depressed fully.
   - If needed, pinch the skin to make sure the injection site is firm.



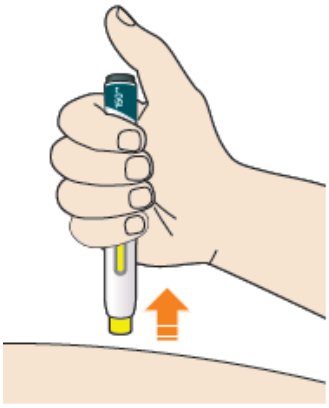
4. **Push and immediately release the grey button with your thumb.**
   - You will hear a click. Your injection has now started.
   - The window will start to turn yellow.

5. **Keep holding the pen against your skin after releasing the button**
   - The injection may take up to 20 seconds.



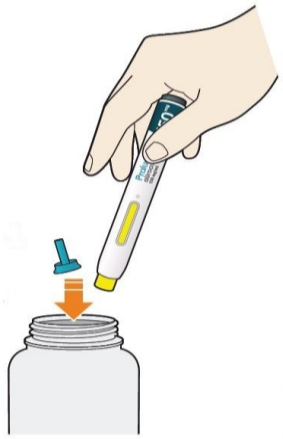
6. **Check the window has turned yellow, before removing the pen.**
   - Do not remove the pen until the entire window has turned yellow.
   - Your injection is complete, when the window has turned completely yellow, you may hear a second click.
   - If the window does not turn completely yellow, call 1-800-265-7927 for help. Do not give yourself a second dose without speaking to your doctor, pharmacist or nurse.

7. **Pull pen away from your skin.**
   - Do not rub the skin after the injection.
   - If you see any blood, press a cotton ball or gauze on the site until the bleeding stops.



8. Discard pen and cap

- Do not put the blue cap back on.
- Throw away the pen in a puncture-resistant container immediately after they have been used
- Dispose of used container according to your local regulations.
- Always keep the container out of the reach of children.



Praluent (alirocumab) 300 mg solution for injection in a pre-filled pen

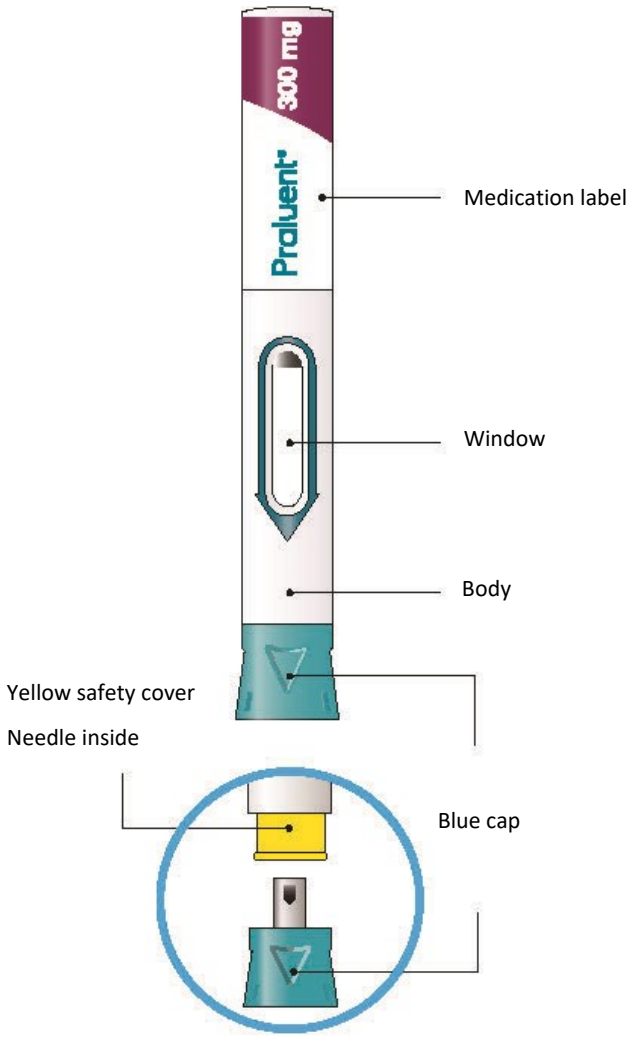
IMPORTANT INFORMATION

- The device is a single use disposable pre-filled pen. It contains 300 mg of Praluent (alirocumab) in 2 mL.
- The Praluent pen contains medicine prescribed by your doctor.
- The medicine is injected under your skin and can be given by yourself or someone else (caregiver).
- It is important that you do not try to give yourself or someone else the injection unless you have received training from your healthcare provider.
- This pen can only be used for one single injection, and must be discarded after use.

Do	Do not
• Keep the Praluent pen out of the sight and reach of children. • Read all of the instructions carefully before using the Praluent pen. • Follow these instructions every time you use a Praluent pen. • Store unused pens in the refrigerator at 36°F to 46°F (2°C to 8°C). For detailed storage conditions see separate patient leaflet for Praluent.	• Do not touch the yellow safety cover. • Do not use the pen if it has been dropped or damaged. • Do not use the pen if the blue cap is missing or not securely attached. • Do not re-use a pen. • Do not shake the pen. • Do not freeze the pen. • Do not expose the pen to extreme heat. • Do not expose the pen to direct sunlight.

Keep this leaflet. If you have questions, ask your doctor, pharmacist or nurse or call the sanofi-aventis number on the patient leaflet.

The parts of the Praluent pen are shown in this picture.



For single use only

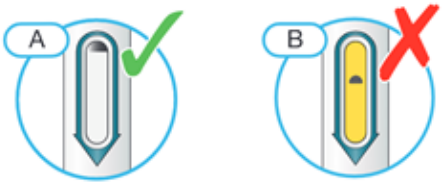
STEP A: GETTING READY FOR AN INJECTION

Before you start you will need:

- the Praluent pen,
- alcohol wipes,
- cotton ball or gauze,
- a puncture-resistant container.

1. **Look at the label on the pen.**
   - Check that you have the correct product and the correct dose.
   - Check the expiration date: do not use if this date has passed.
   - Do not use the Praluent pen if it has been dropped on a hard surface or damaged.

2. **Look at the window.**
   - The liquid should be clear, colourless to pale yellow (see picture A).
   - The liquid should not contain flakes or particles.
   - You may see air bubbles. This is normal.
   - Do not use if the window appears solid yellow (see picture B).
   - Do not use this medicine if the solution is discoloured or cloudy, or if it contains visible flakes or particles.



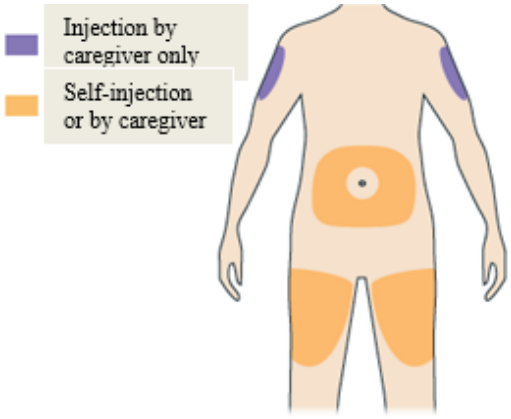
3. **Let the pen warm up at room temperature for 45 minutes.**
   - This is important for administering the entire dose and helps minimize discomfort.
   - Do not heat the pen; let it warm up on its own.
   - Do not put the pen back in the refrigerator.

4. **Prepare the injection site.**
   - Wash your hands with soap and water and dry with a towel.
   - Clean skin in the injection area with an alcohol wipe.
   - You can inject into your (see below picture):
     - thigh
     - belly (except for the 5 cm/2 inch area around your navel)
     - upper arm (to be given by a caregiver only)
   - You can stand or sit to give yourself an injection.

   Important:

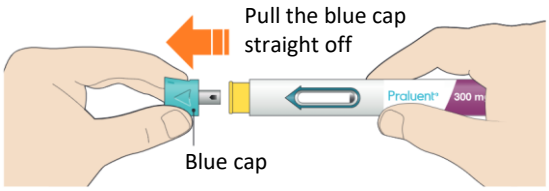
   - Change (rotate) your injection site each time you give yourself an injection.

- If you need to use the same injection area, make sure it is not the same spot on the site you used last time.
- Do not use skin that is tender, hard, red, or hot.
- Do not use any area near a visible vein.

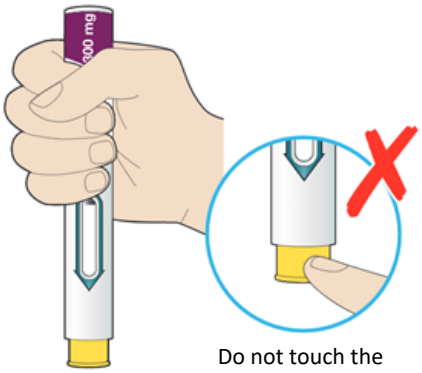


STEP B: HOW TO INJECT

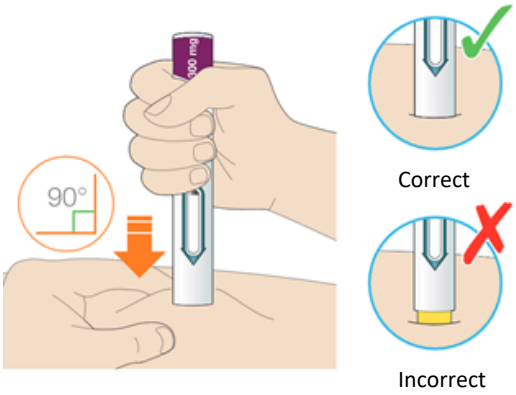
1. **After completing all steps in "STEP A: GETTING READY FOR AN INJECTION", pull off the blue cap.**
   - Do not pull off the cap until you are ready to inject.
   - Do not put the blue cap back on.
   - Do not use the pen if the blue cap is missing or not securely attached.



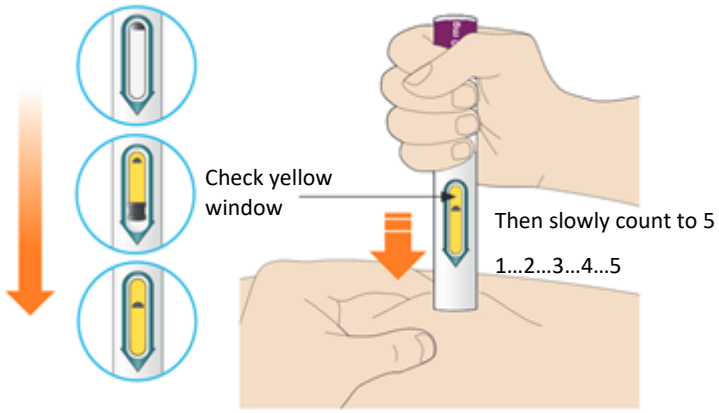
2. **Hold the Praluent pen like this.**
   - Do not touch the yellow safety cover. The needle is inside the yellow safety cover.
   - Make sure you can see the window.
   - Do not press the pen down against your skin until you are ready to inject.



3. **Press the yellow safety cover on your skin at roughly a 90° angle.**
   - Pinch the skin to make sure the injection site is firm.
   - Press the pen straight down against your skin until the yellow safety cover is pushed all the way into the pen and hold (see picture).
   - The injection will not start until the yellow safety cover is fully depressed.
   - There will be a click when the injection starts. The window will start to turn yellow.



4. **Keep holding the pen firmly against your skin.**
   - You may hear a second click.
   - Check that the entire window has turned yellow.
   - Then, slowly count to 5.



5. **Check again that the window has turned yellow, before removing the pen.**
   - If the window does not turn completely yellow, remove the pen and call 1-800-265-7927.
   - Do not give yourself a second injection without speaking to your healthcare provider.

6. **Pull pen away from your skin.**
   - Do not rub the skin after the injection.
   - If you see any blood, press a cotton ball or gauze on the site until the bleeding stops.

7. **Discard pen and cap.**
    - Do not put the blue cap back on.
    - Discard into a puncture-resistant container according to your local regulations.
    - Always keep the container out of the reach and sight of children.