PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PRALUENT®
alirocumab
solution for subcutaneous injection
75 mg/mL and 150 mg/mL
Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor

Sanofi-aventis Canada Inc.
2905 Place Louis-R-Renaud
Laval, Quebec H7V0A3

Submission Control No: 218385

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PRALUENT™
alirocumab

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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<tr>
<th>Route of Administration</th>
<th>Dosage Form / Strength</th>
<th>Nonmedicinal Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous injection</td>
<td>Solution in Pre-filled syringe (PFS) or Pre-filled Pen (PFP) 75 mg/mL 150 mg/mL</td>
<td>Histidine, sucrose, polysorbate 20, water for injection  For a complete listing, see Dosage Forms, Composition and Packaging section</td>
</tr>
</tbody>
</table>

DESCRIPTION

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

INDICATIONS AND CLINICAL USE

Primary hyperlipidemia

PRALUENT (alirocumab) is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).

The effect of PRALUENT on cardiovascular morbidity and mortality has not been determined.

Geriatrics (≥65 years of age):

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 these patients and younger patients but data are limited in patients over 75 years of age (see WARNINGS AND PRECAUTIONS, Special populations, Geriatrics).
Pediatrics (< 18 years of age):

The safety and efficacy in pediatric patients has not been established.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- For contraindications related to concomitant statins or other lipid-modifying therapy (LMT), please refer to their current respective prescribing information.

WARNINGS AND PRECAUTIONS

Concomitant Lipid Lowering Therapies

PRALUENT is used in combination with statins or other lipid lowering therapies (e.g., ezetimibe). The prescriber should refer to the WARNINGS AND PRECAUTIONS sections of the Product Monographs for those medications.

Immune

Hypersensitivity reactions (e.g., pruritus, rash, urticaria), including serious allergic reactions (i.e., hypersensitivity, nummular eczema, hypersensitivity vasculitis) have been reported in PRALUENT clinical studies (see ADVERSE REACTIONS). If signs or symptoms of serious allergic reactions occur, discontinue treatment with PRALUENT, initiate appropriate symptomatic treatment, and monitor until signs and symptoms resolve (see CONTRAINDICATIONS).

Special Populations

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 Part II: 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).

**Nursing Women:**
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.

**Fertility:**
No data are available on the effect of PRALUENT on human fertility. Animal studies did not show any effects on fertility endpoints (see Part II: TOXICOLOGY).

**Pediatrics (< 18 years of age):**
PRALUENT has not been studied in patients less than 18 years of age.

**Geriatrics (≥ 65 years of age):**
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.

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

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

**ADVERSE REACTIONS**

**Adverse Drug 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.
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).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1 - Adverse events occurring in \( \geq 1\% \) of patients treated with PRALUENT and more frequently than with placebo in the pool of placebo-controlled trials

<table>
<thead>
<tr>
<th>Primary System Organ Class</th>
<th>Placebo (N=1276)</th>
<th>Alirocumab (N=2476)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>11.1%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Influenza</td>
<td>4.6%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4.6%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3.8%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2.7%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Gastroenteritis viral</td>
<td>0.7%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.1%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>0.8%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>0.8%</td>
<td>1.0%</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>1.3%</td>
<td>1.4%</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>2.3%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>0.5%</td>
<td>1.2%</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.1%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>0.9%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Gout</td>
<td>0.9%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>
The safety profile of alirocumab in the ezetimibe-controlled study (COMBO II) was comparable to its safety profile in the placebo-controlled studies with no additional adverse reactions identified.

**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 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.

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. The causal relationship between these events and alirocumab has not been established.

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 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/ Anti-drug-antibodies (ADA)
As with all therapeutic proteins, there is a potential for immunogenicity. In phase 3 studies, 4.8% of patients treated with PRALUENT 75 mg or 150 mg Q2W exhibited an ADA response after initiating the treatment as compared to 0.6% in the control group (placebo or ezetimibe) and 1.2% of patients exhibited neutralizing antibodies (NAb), all of them in the alirocumab group. Patients that developed anti-PRALUENT antibodies were more likely to experience injection site reactions than patients treated with PRALUENT who did not develop anti-drug antibodies (10.2% versus 5.9% respectively).

In a separate study (see CLINICAL TRIALS, CHOICE I study), 6.3% of patients treated with PRALUENT 75 mg Q2W or 300 mg every 4 weeks (Q4W) (including some patients with dose adjustment to 150 mg Q2W) exhibited an ADA response as compared to 2.6% of patients treated with placebo. A total of 0.9% of patients in PRALUENT treatment groups developed NAb on at least one occasion. No NAb were observed in patients treated with placebo. The long-term consequences of continuing PRALUENT treatment in the presence of persistent NAb are unknown.
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 these trials, the long-term effects of very low levels of LDL-C induced by PRALUENT are unknown.

**Less Common Clinical Trial Adverse Drug Reactions (<1%)**
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):

- **Infections and infestations:** urinary tract infection (0% vs. 0.1%)
- **Blood and lymphatic system disorders:** neutropenia (<0.1% vs. 0.2%)
- **Immune system disorders:** hypersensitivity (0.1% vs. 0.2%)
- **Metabolism and nutrition disorders:** decreased appetite (<0.1% vs. 0.1%)
- **Nervous system disorders:** hypoesthesia (<0.1% vs. 0.2%)
- **Cardiac disorders:** palpitations (<0.1% vs. 0.2%)
- **Respiratory, thoracic and mediastinal disorders:** epistaxis (<0.1% vs. 0.1%)
- **Gastrointestinal disorders:** abdominal pain (0.1% vs. 0.2%), constipation (0.1% vs. 0.2%)
- **Skin and subcutaneous tissue disorders:** pruritus (0.1% vs. 0.3%), rash (0.1% vs. 0.3%)
- **Musculoskeletal and connective tissue disorders:** muscle spasms (0.4% vs. 0.6%)
- **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%)
- **Investigations:** alanine aminotransferase increased (0.3% vs. 0.4%), gamma-glutamyltransferase increased (<0.1% vs. 0.1%)
- **Injury, poisoning and procedural complications:** accidental overdose (0.5% vs. 0.6%)

**Post-Marketing Experience**

The following adverse reactions have been reported during post-approval use of PRALUENT. The adverse reactions are derived from spontaneous reports and therefore, the frequency is “not known” (cannot be estimated from the available data).
General disorders and administration site conditions
- Flu-like illness

DRUG INTERACTIONS

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

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.

DOSAGE AND ADMINISTRATION

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 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.

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.

**Administration**

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

To administer the 300 mg dose, give two 150 mg PRALUENT injections consecutively at two different injection sites.

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.

**Special Populations**

**Pediatric patients**
Safety and efficacy in pediatric patients has not been established.

**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 ACTION AND 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 ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions – Renal Insufficiency).

**Body weight**
No dose adjustment is needed in patients based on weight (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions – Body Weight).

**OVERDOSAGE**

In controlled clinical studies, no safety issues were identified with more frequent PRALUENT dosing than the recommended Q2W dosing schedule.
ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Alirocumab is a fully human monoclonal antibody that binds with high affinity and specificity to proprotein convertase subtilisin kexin type 9 (PCSK9).

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.

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.

Pharmacokinetics

Absorption:
After subcutaneous (SC) administration of 75 mg to 300 mg alirocumab, median times to maximum serum concentration ($t_{\text{max}}$) 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.

**Excretion:**
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 (<18 years of age):**
PRALUENT has not been studied in pediatric patients.

**Geriatrics (≥65 years of age):**
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.

**Gender:**
Based on a population pharmacokinetic analysis, gender was found not to significantly influence alirocumab pharmacokinetics.

**Race:**
Based on a population pharmacokinetic analysis, race was found not to significantly influence alirocumab pharmacokinetics.

**Body Weight:**
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.

**Hepatic Impairment:**
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 Impairment:**
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.
STORAGE AND STABILITY

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

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

Do not expose to extreme heat.

SPECIAL HANDLING INSTRUCTIONS

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

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

The pre-filled pen (PFP) or pre-filled syringe (PFS) should be allowed to warm to room temperature for 30-40 minutes prior to use. PRALUENT should be used as soon as possible after it has warmed up. Time out of refrigeration should not exceed 24 hours at 25°C.

After use, place the PFP or PFS 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 or PFS 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 PFS or PFP must not be re-used, and instructed in how to safely discard after use.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PRALUENT is a clear, colorless 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) or single-use pre-filled syringe (PFS).
Each 1mL single-use pre-filled pen (PFP) contains 75 mg or 150 mg alirocumab. Each 1mL single-use pre-filled syringe (PFS) contains 75 mg or 150 mg alirocumab.

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

Each 150 mg/mL PFP or PFS 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 PFS or single-use PFP is supplied in a siliconized 1 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 75 or 150 mg PFS: 1, 2, or 6 per carton.
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Alirocumab is a fully human monoclonal antibody (IgG1 isotype) that targets proprotein convertase subtilisin kexin type 9 (PCSK9). 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.
CLINICAL TRIALS

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.

<p>| Table 2 - Summary of trial design and patient demographics for alirocumab clinical trials |
|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|
| Study                                            | Trial design                                                                                     | Dosage, route of administration and duration       | Study subjects (n = number)                        | Mean age (Range)                                  | Gender                                           |
| Placebo-controlled                               | LONG TERM multicenter, randomized, double-blind, placebo-controlled, in patients with HeFH** or non-FH* and on a maximally tolerated dose of statin ± other LMT* |
|                                                  | In addition to stable maximally tolerated daily statin ± other LMT*: - Alirocumab 150 mg Q2W - Placebo 18 months |
|                                                  | Alirocumab: 1553 patients Placebo: 788 patients                                                  | Overall: 60.5 y (18-89) Alirocumab: 60.4 y (18-89) Placebo: 60.6 y (19-87) |
|                                                  | Overall: 62.2% M/37.8% F Alirocumab: 63.3% M/36.7% F Placebo: 60.2% M/39.8% F                |
| COMBO I                                          | multicenter, 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 |
|                                                  | Alirocumab: 209 patients Placebo: 107 patients                                                  | 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                  |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Trial design</th>
<th>Dosage, route of administration and duration</th>
<th>Study subjects (n = number)</th>
<th>Mean age (Range)</th>
<th>Gender</th>
</tr>
</thead>
</table>
| FH I          | multicenter, 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 ³  
- Placebo 18 weeks | Alirocumab: 323 patients  
Placebo: 163 patients | 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         | Multicenter, 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 ³  
- Placebo 18 months | Alirocumab: 167 patients  
Placebo: 82 patients | 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 |
| HIGH FH       | multicenter, 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 patients  
Placebo: 35 patients | 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 |
| Ezetimibe-controlled | COMBO II multicenter, randomized, double-blind, ezetimibe-controlled, in patients at high CV risk with hypercholesterolemia | In addition to statin at maximal tolerated daily dose:  
- Alirocumab | Alirocumab: 479 patients  
Ezetimibe: 241 patients | Overall: 61.6 y (29-88)  
Alirocumab: 61.7 y (30- | Overall: 73.6% M/ 26.4% F  
Alirocumab: 75.2% M/ |
Study design

Trial design

and not at their pre-defined target LDL-C on a maximally tolerated dose of statin

Dosage, route of administration and duration

75mg Q2W, with up-titration to 150 mg Q2W if needed

- Ezetimibe 10 mg QD

2 years

Study subjects (n = number)

Mean age (Range)

Gender

88)

Ezetimibe : 61.3 y (29-84)

24.8% F

Ezetimibe : 70.5% M/ 29.5% F

*LMT: lipid-modifying therapy

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

£ QD: once daily

** HeFH: heterozygous familial hypercholesterolemia

± non-FH : non-familial hypercholesterolemia

**Study results**

**LONG TERM study**

This multicenter, 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 3 and Figure 2).
Table 3 - Mean percent Change from Baseline and Difference\textsuperscript{a} from Placebo in Lipid Parameters at Week 12 and Week 24 in the LONG TERM Study\textsuperscript{b}

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>LDL-C</th>
<th>Total-C</th>
<th>Non-HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 12</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1.3</td>
<td>0.1</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>PRALUENT (150 mg)</td>
<td>-61.4</td>
<td>-37.7</td>
<td>-52.3</td>
<td>-53.8</td>
</tr>
<tr>
<td>Difference from placebo (LS mean\textsuperscript{c}) (95%CI)</td>
<td>-62.7 (-65.2, -60.3)</td>
<td>-37.8 (-39.4, -36.3)</td>
<td>-53.0 (-55.1, -50.9)</td>
<td>-54.2 (-56.6, -51.9)</td>
</tr>
<tr>
<td>p value\textsuperscript{d}</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Week 24</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.7</td>
<td>-0.3</td>
<td>0.6</td>
<td>1.1</td>
</tr>
<tr>
<td>PRALUENT (150 mg)</td>
<td>-57.8</td>
<td>-36.0</td>
<td>-49.1</td>
<td>-49.8</td>
</tr>
<tr>
<td>Difference from placebo (LS mean\textsuperscript{c}) (95%CI)</td>
<td>-58.5 (-61.1, -55.8)</td>
<td>-35.7 (-37.4, -34.0)</td>
<td>-49.7 (-52.0, -47.4)</td>
<td>-50.9 (-53.3, -48.4)</td>
</tr>
<tr>
<td>p value\textsuperscript{d}</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Difference is PRALUENT minus placebo
\textsuperscript{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.
\textsuperscript{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.
\textsuperscript{d} A hierarchical testing procedure was used to test the primary and the key secondary efficacy endpoints while controlling for Type I error rate.
**COMBO I study**

A multicenter, 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 4).

Table 4 - Mean percent Change from Baseline and Differencea from Placebo in Lipid Parameters at Week 12 and Week 24 in the COMBO I Studyb

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>LDL-C</th>
<th>Total-C</th>
<th>Non-HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 12</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1.1</td>
<td>0.9</td>
<td>2.5</td>
<td>3.2</td>
</tr>
<tr>
<td>PRALUENT (75 mg)</td>
<td>-44.9</td>
<td>-24.7</td>
<td>-36.3</td>
<td>-33</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>-46</td>
<td>-25.6</td>
<td>-38.8</td>
<td>-36.2</td>
</tr>
<tr>
<td>(LS meanc) (95%CI)</td>
<td>(-52.6, -39.5)</td>
<td>(-30.4, -20.7)</td>
<td>(-45.2, -32.4)</td>
<td>(-42.1, -30.2)</td>
</tr>
<tr>
<td>p valued</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Week 24</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>-1.5</td>
<td>-2.3</td>
<td>-1.1</td>
<td>0.2</td>
</tr>
<tr>
<td>PRALUENT (75/up to 150 mg)</td>
<td>-44.2</td>
<td>-25.6</td>
<td>-36.0</td>
<td>-33.6</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>-42.7</td>
<td>-23.3</td>
<td>-34.8</td>
<td>-33.8</td>
</tr>
<tr>
<td>(LS meanc) (95%CI)</td>
<td>(-49.9, -35.4)</td>
<td>(-27.9, -18.7)</td>
<td>(-41.3, -28.3)</td>
<td>(-39.9, -27.7)</td>
</tr>
<tr>
<td>p valued</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

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 multicenter, 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 5 and Figure 3). 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 5 and Figure 4)
Table 5 - Mean Percent Change from Baseline and Difference\textsuperscript{a} from Placebo in Lipid Parameters at Week 12 and Week 24 in Studies FH I\textsuperscript{b} and FH II\textsuperscript{c}

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

\textsuperscript{a} Difference is PRALUENT minus placebo
\textsuperscript{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.
\textsuperscript{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.
\textsuperscript{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 FH I Study$^a$

![Graph showing LDL-C percent change from baseline over 52 weeks]

Placebo (N)$^b$ 163  149  146
PRALUENT (N)$^b$ 323  290  277

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

Number of patients with observed data

**HIGH FH study**
HIGH FH was a multicenter, 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 6).

Table 6 - Mean percent Change from Baseline and Differencea from Placebo in Lipid Parameters at Week 12 and Week 24 in the HIGH FH Studyb

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>LDL-C</th>
<th>Total-C</th>
<th>Non-HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>-6.7</td>
<td>-5.1</td>
<td>-7.0</td>
<td>-9.1</td>
</tr>
<tr>
<td>PRALUENT (150 mg)</td>
<td>-46.9</td>
<td>-33.2</td>
<td>-41.8</td>
<td>-39.3</td>
</tr>
<tr>
<td>Difference from placebo (LS meanc) (95%CI)</td>
<td>-40.3 (-51.3, -29.2)</td>
<td>-28.1 (-36.3, -19.8)</td>
<td>-34.8 (-45.0, -24.6)</td>
<td>-30.2 (-39.2, -21.3)</td>
</tr>
<tr>
<td>p valued</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Week 24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>-6.9</td>
<td>-4.8</td>
<td>-6.2</td>
<td>-8.6</td>
</tr>
<tr>
<td>PRALUENT (150 mg)</td>
<td>-43.3</td>
<td>-31.3</td>
<td>-39.7</td>
<td>-36.5</td>
</tr>
<tr>
<td>Difference from placebo (LS meanc) (95%CI)</td>
<td>-36.3 (-48.5, -24.2)</td>
<td>-26.5 (-35.5, -17.4)</td>
<td>-33.5 (-44.2, -22.7)</td>
<td>-28.0 (-37.6, -18.3)</td>
</tr>
<tr>
<td>p valued</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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.

**COMBO II study**

COMBO II study was a 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 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. 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).

**CHOICE I**

CHOICE I was a double-blind, placebo-controlled 48-week trial that randomly assigned 312 patients to PRALUENT 300 mg every 4 week dosing regimen (Q4W), 78 patients to PRALUENT 75 mg every 2 weeks (Q2W), and 157 patients to placebo. All 547 patients had hypercholesterolemia (8% HeFH, 92% non-FH) and taking concomitant statin therapy. 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 62 years (range 21-88), 37% were women, 88% were Caucasian, 10% were Black, and 2% were Hispanic/Latino. Overall, 64% of patients had atherosclerotic cardiovascular disease. The mean LDL-C at baseline was 2.92 mmol/L (113 mg/dL). The proportion of patients who discontinued study drug prior to the 24-week endpoint was 9% among those treated with PRALUENT 300 mg Q4W, 13% among those treated with PRALUENT 75 mg Q2W and 13% among those treated with placebo.

At week 12, the treatment difference in mean LDL-C percent change was -54% (97.5% CI: -61%, -48%) between PRALUENT 300 mg Q4W and placebo and -44% (97.5% CI: -53%, -35%) between PRALUENT 75 mg Q2W and placebo (Figure 5).

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%).
Figure 5 – Mean percent Change from Baseline in LDL-C up to week 12 in CHOICE I study – patients on concomitant statin treated with PRALUENT 75 mg Q2W, PRALUENT 300 mg Q4W or placebo

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

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

Alirocumab binds with high affinity to PCSK9 across several species and blocks its interaction with LDLR in vitro and in vivo. The administration of alirocumab significantly reduced levels of serum LDL-C in rats and cynomolgus monkeys in a dose-dependent manner. Reductions in serum LDL-C were more pronounced in cynomolgus monkeys when administered in combination with atorvastatin. Species specific reductions in HDL-C were observed in rats and in cynomolgus monkeys only when combined with atorvastatin.

Pharmacokinetics

Alirocumab displayed nonlinear pharmacokinetics in the rat and monkey, which were characterized by saturable, target-mediated disposition. An approximate 2- to 3-fold accumulation of total alirocumab generally occurred in both species with repeated weekly intravenous and subcutaneous dosing in the majority of studies, with achievement of steady state typically observed after 5 alirocumab doses. The absolute bioavailability of alirocumab following subcutaneous administration was dose independent and ranged from 44% to 65% in
the rat and from 73% to 77% in the monkey. Alirocumab crossed the placental barrier, as
determined by measurable serum total alirocumab concentrations in fetal rats and infant
monkeys. In monkeys, repeated concomitant administration of alirocumab with atorvastatin did
not influence the pharmacokinetics of atorvastatin or its active metabolites, but showed a trend
towards reduced alirocumab exposure.

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.
REFERENCES


READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrPRLUENT®

alirocumab

solution for subcutaneous injection
75 mg/mL and 150 mg/mL

Read this carefully before you start taking PRLUENT 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 PRLUENT.

What is PRLUENT used for?

PRLUENT is used along with diet and maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia (an inherited condition that causes high levels of low density lipoprotein cholesterol [LDL-C]), or atherosclerotic heart problems (such as heart attacks or strokes), who need additional lowering of LDL cholesterol.

The effect of PRLUENT on heart problems such as heart attacks, stroke, or death is not known. It is not known if PRLUENT is safe and effective in children.

How does PRLUENT work?

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

- PRLUENT 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.
- PRLUENT 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 PRLUENT?

Medicinal ingredients: alirocumab
Non-medicinal ingredients: histidine, polysorbate 20, sucrose and water for injection
PRALUENT comes in the following dosage forms:

- Pre-filled pen
- Pre-filled syringe

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, talk to your healthcare professional before you take PRALUENT. Talk about any health conditions or problems you may have, including if you:

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

Other warnings you should know about:

There is no experience with PRALUENT 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 or pre-filled syringe to make sure you have the correct product and the correct strength of PRALUENT before each 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), or as a single-dose pre-filled syringe. Your healthcare provider will prescribe the type and 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 or pre-filled syringe**

Before you use the pre-filled pen or the pre-filled syringe 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 or the pre-filled syringe as described in the “Instructions for Use”.

**Usual dose:**

PRALUENT is available as 75 mg or 150 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 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. 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, a swollen face, 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-colored spots on the skin, diarrhea.
- Hives (urticaria)
- Reddish skin spots, sometimes with blisters (nummular eczema)

### Serious side effects and what to do about them

<table>
<thead>
<tr>
<th>Symptom / effect</th>
<th>Talk to your healthcare professional</th>
<th>Stop taking drug and get immediate medical help</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Only if severe</td>
<td>In all cases</td>
</tr>
<tr>
<td><strong>RARE</strong> (may affect up to 1 in 1,000 people)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity vasculitis, which is a specific form of allergic reaction. Symptoms may include diarrhea, rash, or purple-colored spots on the skin (purpura)</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

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 or the syringe 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 (in 30 to 40 min). When taken out of the refrigerator to warm up the pen or the syringe, do not put near a heat source or in direct sunlight. Do not keep PRALUENT for more than 24 hours at room temperature.

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

After use, put the pen or the syringe 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer’s website: www.sanofi.ca, or by calling 1-800-265-7927.
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.

<table>
<thead>
<tr>
<th>Do</th>
<th>Do not</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep the PRALUENT pen out of the reach of children.</td>
<td>Do not touch the yellow safety cover.</td>
</tr>
<tr>
<td>Read all of the instructions carefully before using the PRALUENT pen.</td>
<td>Do not use the pen if it has been dropped or damaged.</td>
</tr>
<tr>
<td>Follow these instructions every time you use a PRALUENT pen.</td>
<td>Do not use the pen if the blue cap is missing or not securely attached.</td>
</tr>
<tr>
<td>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.</td>
<td>Do not re-use a pen.</td>
</tr>
<tr>
<td></td>
<td>Do not shake the pen.</td>
</tr>
<tr>
<td></td>
<td>Do not freeze the pen.</td>
</tr>
<tr>
<td></td>
<td>Do not expose the pen to extreme heat.</td>
</tr>
<tr>
<td></td>
<td>Do not expose the pen to direct sunlight.</td>
</tr>
</tbody>
</table>

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.
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, colorless 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 discolored 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

![Injection Sites](image)

**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.

![Image of a hand holding a PRALUENT pen]

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.

![Image showing correct angle for pressing the yellow safety cover]

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.

![Image showing the green button being pushed]
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.

![Image of pen being pulled away](image1)

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.

![Image of pen being discarded](image2)
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.

<table>
<thead>
<tr>
<th>Do</th>
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<tbody>
<tr>
<td>Keep the PRALUENT pen out of the reach of children.</td>
<td>Do not touch the yellow safety cover.</td>
</tr>
<tr>
<td>Read all of the instructions carefully before using the PRALUENT pen.</td>
<td>Do not use the pen if it has been dropped or damaged.</td>
</tr>
<tr>
<td>Follow these instructions every time you use a PRALUENT pen.</td>
<td>Do not use the pen if the blue cap is missing or not securely attached.</td>
</tr>
<tr>
<td>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.</td>
<td>Do not re-use a pen.</td>
</tr>
<tr>
<td></td>
<td>Do not shake the pen.</td>
</tr>
<tr>
<td></td>
<td>Do not freeze the pen.</td>
</tr>
<tr>
<td></td>
<td>Do not expose the pen to extreme heat.</td>
</tr>
<tr>
<td></td>
<td>Do not expose the pen to direct sunlight.</td>
</tr>
</tbody>
</table>

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.
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, colorless 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 discolored 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.

![Image of the PRALUENT pen held in a hand]

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.

![Images showing correct and incorrect angles for pressing the yellow safety cover]

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) 75 MG SOLUTION FOR INJECTION IN A PRE-FILLED SYRINGE

IMPORTANT INFORMATION

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

<table>
<thead>
<tr>
<th>Do</th>
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</thead>
<tbody>
<tr>
<td>Keep the PRALUENT syringe out of the reach of children.</td>
<td>Do not touch the needle.</td>
</tr>
<tr>
<td>Read all of the instructions carefully before using the PRALUENT syringe.</td>
<td>Do not use the syringe if it has been dropped or damaged.</td>
</tr>
<tr>
<td>Follow these instructions every time you use a PRALUENT syringe.</td>
<td>Do not use the syringe if the gray needle cap is missing or not securely attached.</td>
</tr>
<tr>
<td>Store unused syringes 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.</td>
<td>Do not re-use a syringe.</td>
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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 syringe are shown in this picture.
STEP A: GETTING READY FOR AN INJECTION

Before you start you will need:
  • the PRALUENT syringe,
  • alcohol wipes,
  • cotton ball or gauze,
  • a puncture-resistant container (see STEP B-6).

1. **Before you start.**
   • Take the syringe out of the packaging by holding the syringe body.
2. **Look at the label on the syringe.**
   - Check that you have the correct product and the correct dose (green plunger for 75 mg/ml). Check the use by date - do not use if this date has passed.
   - Check the liquid is clear, colorless to pale yellow and free from particles - if not, do not use.
   - Check that the syringe is not open or damaged.

3. **Let the syringe 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 syringe, let it warm up on its own.
   - Use the syringe as soon as possible after it has warmed up.
   - Do not put the syringe 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 needle cap.
   • Do not pull off the cap until you are ready to inject.
   • Hold the syringe in the middle of the syringe body with the needle pointing away from you.
   • Keep your hand away from the plunger.
   • Do not get rid of any air bubbles in the syringe before the injection.
   • Do not put the grey cap back on.

2. If needed pinch the skin.
   • Use your thumb and first finger to pinch a fold of skin at the injection site.
   • Hold the skin like this for the whole injection.
3. **Insert the needle into the fold of skin with a quick dart-like motion.**
   - Use a 90° angle if you can pinch 5 cm/2 inches of skin.
   - Use a 45° angle if you can only pinch 2 cm/1 inch of skin.

![Image of needle insertion at 90° and 45° angles]

4. **Push the plunger down.**
   - Inject all of the solution by slowly and steadily pushing down the plunger.

![Image of plunger being pushed down]

5. **Before you remove the needle check the syringe is empty.**
   - Do not remove the syringe until it is completely empty.
   - Pull the needle out of the skin at the same angle as it was inserted.
   - 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.
6. **Discard syringe and cap**
   - Do not put the grey needle cap back on.
   - Do not re-use the syringe.
   - Throw away the syringe and the cap 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 SYRINGE

IMPORTANT INFORMATION

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

<table>
<thead>
<tr>
<th>Do</th>
<th>Do not</th>
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<tr>
<td>Keep the PRALUENT syringe out of the reach of children.</td>
<td>Do not touch the needle.</td>
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<tr>
<td>Read all of the instructions carefully before using the PRALUENT syringe.</td>
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<td>Follow these instructions every time you use a PRALUENT syringe.</td>
<td>Do not use the syringe if the gray needle cap is missing or not securely attached.</td>
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- the PRALUENT syringe,
- alcohol wipes,
- cotton ball or gauze,
- a puncture-resistant container (see STEP B-6).

1. Before you start.
   - Take the syringe out of the packaging by holding the syringe body.
2. **Look at the label on the syringe.**
   - Check that you have the correct product and the correct dose (gray plunger for 150 mg/ml). Check the use by date - do not use if this date has passed.
   - Check the liquid is clear, colorless to pale yellow and free from particles - if not, do not use.
   - Check that the syringe is not open or damaged.

3. **Let the syringe 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 syringe, let it warm up on its own.
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