If an every-4-week dose is missed, instruct the patient to administer the injection within the original schedule. If the missed scheduled dosing date, Reassess LDL-C within 4 to 8 weeks.

Dosage and Administration

The recommended starting dose of PRALUENT is 75 mg once every 2 weeks administered subcutaneously, since the majority of patients achieve sufficient LDL-C reduction with this dosage. An alternative starting dosage for patients who prefer less frequent dosing is 300 mg once every 4 weeks (monthly). (2.1)

For patients receiving PRALUENT 300 mg every 4 weeks, measure LDL-C just prior to the next scheduled dose. If the LDL-C response is inadequate, the dosage may be adjusted to the maximum dosage of 150 mg administered every 2 weeks. (2.1)

1.1 Primary Hyperlipidemia

PRALUENT® 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, who require additional lowering of LDL-cholesterol (LDL-C). (1.1)

Contraindications

History of a serious hypersensitivity reaction to PRALUENT. (4)

Adverse Reactions

The most commonly occurring adverse reactions (≥5% of patients treated with PRALUENT and occurring more frequently than with placebo) are nasopharyngitis, injection site reactions, and influenza. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 08/2018

The recommended dose of PRALUENT in patients with HeFH undergoing LDL apheresis is 150 mg once every 2 weeks. PRALUENT can be administered without regard to timing of apheresis. (2.1)

Dose and Administration

Instruct the patient to administer the injection within 7 days from 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.

8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed
3 DOSE FORMS AND STRENGTHS
PRALUENT is a clear, colorless to pale yellow solution available as follows:
Injection: Single-dose pre-filled pen
• 75 mg/mL
• 150 mg/mL
Injection: Single-dose pre-filled syringe
• 75 mg/mL
• 150 mg/mL

4 CONTRAINDICATIONS
PRALUENT is contraindicated in patients with a history of a serious hypersensitivity reaction to PRALUENT. Reactions have included hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization. [See Warnings and Precautions (5.1).]

5 WARNINGS AND PRECAUTIONS
5.1 Allergic Reactions
Hypersensitivity reactions (e.g., pruritus, rash, urticaria), including some serious events (e.g., hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization), have been reported with PRALUENT treatment. If signs or symptoms of serious allergic reactions occur, discontinue treatment with PRALUENT, treat according to the standard of care, and monitor until signs and symptoms resolve [see Contraindications (4)].

6 ADVERSE REACTIONS
The following adverse reactions are also discussed in the other sections of the labeling:
• Allergic Reactions [See Warnings and Precautions (5.1)].

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The safety of PRALUENT was evaluated in 9 placebo-controlled trials that included 2476 patients treated with PRALUENT 75 mg and/or 150 mg every 2 weeks, including 2133 exposed for 6 months and 1999 exposed for more than 1 year (median treatment duration of 65 weeks). The mean age of the population was 59 years, 40% of the population were women, 90% were Caucasians, 4% were Black or African American, and 3% were Asians. At baseline, 37% of patients had a diagnosis of heterozygous familial hypercholesterolemia and 66% had clinical atherosclerotic cardiovascular disease.

Table 1: Adverse Reactions Occurring in Greater Than or Equal to 2% of PRALUENT-Treated Patients and More Frequently Than with Placebo

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N=1276)</th>
<th>PRALUENT* (N=2476)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>11.1%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Injection site reactions*</td>
<td>5.1%</td>
<td>7.2%</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>Diarrhea</td>
<td>4.4%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3.8%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3.4%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Muscle pains</td>
<td>2.4%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2.7%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Cough</td>
<td>2.3%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Contusion</td>
<td>1.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>1.6%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

*75 mg every 2 weeks and 150 mg every 2 weeks combined
†Includes erythema/redness, itching, swelling, pain/tenderness

Adverse reactions led to discontinuation of treatment in 5.3% of patients treated with PRALUENT and 5.1% of patients treated with placebo. 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 elevated liver enzymes (0.3% versus <0.1%).

Local Injection Site Reactions
In a pool of placebo-controlled trials evaluating PRALUENT 75 mg and/or 150 mg administered every 2 weeks (Q2W), local injection site reactions including erythema/redness, itching, swelling, and pain/tenderness were reported more frequently in patients treated with PRALUENT (7.2% versus 5.1% for PRALUENT and placebo, respectively).

Few patients discontinued treatment because of these reactions (0.2% versus 0.4% for PRALUENT and placebo, respectively), but patients receiving PRALUENT had a greater number of injection site reactions, had more reports of associated symptoms, and had reactions of longer average duration than patients receiving placebo.

In a 48-week placebo-controlled trial evaluating PRALUENT 300 mg every 4 weeks (Q4W) and 75 mg Q2W, in which all patients received an injection of drug or placebo every 2 weeks to maintain the blind, 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). Three patients (0.7%) treated with PRALUENT 300 mg Q4W discontinued treatment due to local injection site reactions. There were no patients (0%) in the other 2 treatment groups.

Allergic Reactions
Adverse reactions were reported more frequently in patients treated with PRALUENT than in those treated with placebo (6.6% versus 7.8%). The proportion of patients who discontinued treatment due to allergic reactions was higher among those treated with PRALUENT (0.6% versus 0.2%). Serious allergic reactions, such as hypersensitivity, nummular eczema, and hypersensitivity vasculitis were reported in patients using PRALUENT in controlled clinical trials [see Warnings and Precautions (5.1)].

Neurocognitive Events
Neurocognitive events were reported in 0.8% of patients treated with PRALUENT and 0.7% of patients treated with placebo. Confusion or memory impairment were reported more frequently by those treated with PRALUENT (0.2% for each) than in those treated with placebo (<0.1% for each).

Liver Enzyme Abnormalities
Dyslipidemia disorders (primarily related to abnormalities in liver enzymes) were reported in 2.5% of patients treated with PRALUENT and 1.8% of patients treated with placebo, leading to treatment discontinuation in 0.4% and 0.2% of patients, respectively. Increases in serum transaminases to greater than 3 times the upper limit of normal occurred in 1.7% of patients treated with PRALUENT and 1.4% of patients treated with placebo.

Low LDL-C Values
In the placebo-controlled and active-controlled clinical trials using an every 2 week or every 4 week dosing interval, 914 PRALUENT-treated patients had two consecutive calculated LDL-C values that were <25 mg/dL, and 281 patients had LDL-C values <15 mg/dL. LDL-C values <25 mg/dL, and <15 mg/dL were observed more frequently in patients treated with the PRALUENT 150 mg Q2W or 300 mg Q4W dosing regimens. Changes to background lipid-lowering therapy (e.g., maximally tolerated statins) were not made in response to low LDL-C values, and PRALUENT dosing was not modified or interrupted on this basis.

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.

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity with PRALUENT. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) formation and its possible clinical significance may vary for different assays, sample methodologies, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PRALUENT in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In a pool of 9 placebo-controlled and active-controlled trials, 4.8% (147/3033) of patients treated with PRALUENT 75 mg and/or 150 mg every 2 weeks (Q2W) had anti-drug antibodies (ADA) newly detected at least once after initiating treatment compared with 0.6% (10/1708) of patients treated with control. For 1.9% (57/3033) of patients treated with PRALUENT and 0.5% (8/1708) of patients treated with control, ADA were detected in at least 2 samples separated by at least 12 weeks or were detected only at the last sampling time point. Patients treated with PRALUENT 75 mg and/or 150 mg Q2W who ever developed ADA had a higher incidence of injection site reactions compared with patients who never had ADA detected (10.2% vs 5.9%). In the same pool, 1.2% (36/3033) of patients treated with PRALUENT 75 mg and/or 150 mg Q2W had neutralizing antibodies (NAB) newly detected at least once, and 0.3% (9/3033) of patients treated with PRALUENT exhibited some attenuation in efficacy. No patients treated with control developed NAb. The long-term consequences of continuing PRALUENT treatment in the presence of persistent NAb are unknown.

In a separate clinical study of patients treated with PRALUENT 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 qualitatively similar to the results from the pooled trials described above.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to PRALUENT during pregnancy. Please contact 1-877-311-8972 or go to https://mothertobaby.org/ongoing-study/praluent/ to enroll in or to obtain information about the registry.

Risk Summary
There are no available data on use of PRALUENT in pregnant women to inform a drug-associated risk. In animal reproduction studies, there were no effects on embryo-fetal development when rats were subcutaneously administered alirocumab during organogenesis at dose exposures up to 12-fold the exposure at the maximum recommended human dose of 150 mg every two weeks. In monkeys, suppression of the humoral immune response was observed in infant monkeys when alirocumab was dosed during organogenesis to parturition at dose exposures 13-fold the exposure at the maximum recommended human dose of 150 mg every two weeks. In a toxicology study, female monkeys were dosed with alirocumab at 15 mg/kg/week and 75 mg/kg/week for 4 weeks, with weekly serum samples collected and assayed for neutralizing antibodies (Nab). There was no association between serum alirocumab concentrations and neutralizing antibodies. For the highest dose group of 75 mg/kg/week, there was a trend for higher neutralizing antibodies, but this was not statistically significant. In Sprague Dawley rats, no effects on embryo-fetal development were observed when alirocumab was dosed at up to 75 mg/kg/dose by the subcutaneous route on gestation days 6 and 12 at exposures 12-fold the maximum recommended human dose of 150 mg every two weeks. In a study in cynomolgus monkeys, suppression of the humoral immune response to keyhole limpet hemocyanin (KLH) antigen was observed in infant monkeys at 4 to 6 months of age when alirocumab was dosed during organogenesis to parturition at 15 mg/kg/week and 75 mg/kg/week by the subcutaneous route, corresponding to 13-fold and 81-fold the human
exposure at the maximum recommended human dose of 150 mg every two weeks, based on serum AUC. The lower dose tested in the monkey resulted in hepatic immune suppression; therefore it is unknown if this effect would be observed at clinical exposure. No study designed to challenge the immune system of infant monkeys was conducted. No additional embryo-fetal, prenatal or postnatal effects were observed in infant monkeys, and no maternal effects were observed. When given to rats, alirocumab was dosed at up to 75 mg/kg/week by the subcutaneous route, corresponding to maternal exposure of 81-fold the exposure at the maximum recommended human dose of 150 mg every two weeks, based on serum AUC.

8.2 Lactation
Risk Summary

There is no information regarding the presence of alirocumab in human milk, the effects on the breastfed infant, or the effects on milk production. The development and health benefits of breastfed children should be considered along with the mother’s clinical need for PRALUENT and any potential adverse effects on the breastfed infant from PRALUENT or from the underlying maternal condition. Human IgG is present in human milk, but published data suggest that breastmilk IgG antibodies do not enter the neonatal and infant circulation in substantial amounts.

8.4 Pediatric Use
Safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use
In controlled studies, 1158 patients treated with PRALUENT were ≥65 years of age and 241 patients treated with PRALUENT were ≥75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 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 Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment
No dose adjustment is needed for patients with mild or moderate hepatic impairment. No data are available in patients with severe hepatic impairment. [See Clinical Pharmacology (12.3)].

11 DESCRIPTION
Alirocumab is a human monoclonal antibody that targets proprotein convertase subtilisin kexin type 9 (PCSK9). Alirocumab is a PCSK9 inhibitor produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture. Alirocumab consists of two disulfide-linked heavy human chains, each covalently linked through a disulfide bond to a 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.

PRALUENT is a sterile, preservative-free, clear, colorless to pale yellow solution for subcutaneous injection. PRALUENT 75 mg/mL or 150 mg/mL solution for subcutaneous injection in a single-dose pre-filled pen or single-dose pre-filled syringe is supplied in a siliconized 1 mL Type-1 clear glass syringe. The needle shield is not made with natural rubber latex.

Each 75 mg/mL pre-filled pen or pre-filled syringe contains 75 mg alirocumab, histidine (8 mM), polysorbate 20 (0.1 mg), sucrose (100 mg), and Water for Injection USP, to pH 6.0.

Each 150 mg/mL pre-filled pen or pre-filled syringe contains 150 mg alirocumab, histidine (6 mM), polysorbate 20 (0.1 mg), sucrose (100 mg), and Water for Injection USP, to pH 6.0.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Alirocumab is a human monoclonal antibody that binds to proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 inhibits hepatic liver conversion of low-density lipoprotein cholesterol (LDL-C) metabolism. Alirocumab is a human monoclonal antibody that binds to the liver enzyme proprotein convertase subtilisin kexin type 9 (PCSK9), reducing hepatic LDL receptor degradation and increasing plasma LDL-C levels.

12.2 Pharmacokinetics
Absorption
After subcutaneous (SC) administration of 75 mg to 300 mg alirocumab, median times to maximum serum concentrations (tmax) were 3–7 days. The pharmacokinetics 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 pharmacokinetics analysis. A slightly greater than dose proportional increase was observed with a 2.1-fold 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 dose normalized exposure with 300 mg every 4 weeks treatment was proportional increase was observed, with a 2.1-fold to 2.7-fold increase in total alirocumab.

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 and Elimination
Specific metabolism studies were not conducted, because alirocumab is a protein. Alirocumab is expected to degrade to small peptides and individual amino acids. 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, indicating that cytochrome P450 enzymes (mainly CYP3A4 and CYP2C9) and transporter proteins such as P-gp and OATP were not affected by alirocumab.

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.

Specific Populations
A population pharmacokinetic analysis was conducted on data from 2799 subjects. Age, body weight, gender, race, and creatinine clearance were found not to significantly influence alirocumab pharmacokinetics. No dose adjustments are recommended for these demographics.

Pediatric
PRALUENT has not been studied in pediatric patients [see Use in Specific Populations (8.4)].

11.3 Pharmacokinetics
PRALUENT has not been studied in pediatric patients [see Use in Specific Populations (8.4)].

12.3 Animal Toxicology and/or Pharmacology

During a 13-week toxicology study of 75 mg/kg once weekly alirocumab in combination with 40 mg/kg once daily atorvastatin in adult monkeys, there were no effects on surrogate markers of fertility (e.g., estrus cyclicity, testicular volume, ejaculate volume, sperm motility, or total sperm count per ejaculate) in a 6-month chronic toxicology study in sexually-mature monkes subcutaneously administered at 5, 15, and 75 mg/kg/week at systemic exposures up to 103-fold the 150 mg every 2 weeks subcutaneous clinical dose based on serum AUC. In addition, there were no adverse alirocumab-related anatomic pathology or histopathology findings in reproductive tissues in rat or monkey toxicology studies at systemic exposures up to 11-fold and 103-fold respectively, in the 6-month studies, compared to clinical systemic exposure following a 150 mg every two weeks dose, based on serum AUC.

13 CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenicity studies have not been conducted with alirocumab. The mutagenic potential of alirocumab has not been evaluated; however, monoclonal antibodies are not expected to alter DNA or chromosmes.

There were no adverse effects on surrogate markers of fertility (e.g., estrus cyclicity, testicular volume, ejaculate volume, sperm motility, or total sperm count per ejaculate) in a 6-month chronic toxicology study in sexually-mature monkes subcutaneously administered at 5, 15, and 75 mg/kg/week at systemic exposures up to 103-fold the 150 mg every 2 weeks subcutaneous clinical dose based on serum AUC. In addition, there were no adverse alirocumab-related anatomic pathology or histopathology findings in reproductive tissues in rat or monkey toxicology studies at systemic exposures up to 11-fold and 103-fold respectively, in the 6-month studies, compared to clinical systemic exposure following a 150 mg every two weeks dose, based on serum AUC.

In 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).

Three studies used an initial dose of 75 mg every 2 weeks (Q2W) followed by criteria-based up-titraton to 150 mg Q2W at week 12 for patients who did not achieve their pre-defined target LDL-C at week 8. The majority of patients (57% to 83%) who were treated for at least 12 weeks did not require up-titration. Two studies used only a 150 mg Q2W dose.

A sixth double-blind, placebo-controlled, 48-week trial 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 primary efficacy endpoint was measured at week 24 (mean percent change in LDL-C from baseline).

A seventh double-blind, placebo-controlled trial was conducted in 62 patients with HeFH who received PRALUENT 150 mg Q2W or placebo.

Study 1 was a multicenter, double-blind, placebo-controlled trial that randomly assigned 1553 patients to PRALUENT 150 mg Q2W and 788 patients to placebo. All patients were taking maximally tolerated doses of statin with or without other lipid-modifying therapy, and required additional LDL-C reduction. The mean age was 61 years (range 18-89), 36% were women, 93% were Caucasian, 1% were Black, and 5% were Hispanic/Latino. Overall, 69% were non-FH patients with clinical atherosclerotic cardiovascular disease and 18% had HeFH. The average LDL-C at baseline was 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% (95% CI: -61%, -56%; p-value: <0.0001).

For additional results see Table 2 and Figure 1.

3
Table 2: Mean Percent Change from Baseline and Difference* from Placebo in Lipid Parameters at Week 24 in Study 1

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>LDL-C (Mean Percent Change from Baseline)</th>
<th>Total-C</th>
<th>Non-HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo 150 mg</td>
<td>-58</td>
<td>-36</td>
<td>-49</td>
<td>-50</td>
</tr>
<tr>
<td>Placebo</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PRALUENT (150 mg)</td>
<td>-58</td>
<td>-36</td>
<td>-49</td>
<td>-50</td>
</tr>
<tr>
<td>Difference from placebo (LS Mean) (95% CI)</td>
<td>-58 (-61, -56)</td>
<td>-36 (-37, -34)</td>
<td>-50 (-52, -47)</td>
<td>-51 (-53, -48)</td>
</tr>
</tbody>
</table>

* Difference is PRALUENT minus Placebo

†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.

Study 2 was a multicenter, double-blind, placebo-controlled trial that randomly assigned 209 patients to PRALUENT and 107 patients to placebo. Patients were taking maximally tolerated doses of statins with or without other lipid-modifying therapy, and required additional LDL-C reduction.

The mean age was 63 years (range 39–87); 34% were women, 82% were Caucasian, 16% were Black, and 11% were Hispanic/Latino. Overall, 84% had clinical atherosclerotic cardiovascular disease. Mean baseline LDL-C was 102 mg/dL.

Overall, 45% of these patients with HeFH also had clinical atherosclerotic cardiovascular disease. The average LDL-C at baseline was 141 mg/dL.

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 12, the mean percent change from baseline in LDL-C was -45% with PRALUENT compared to 1% with placebo, and the treatment difference between PRALUENT 75 mg Q2W and placebo in mean LDL-C percent change was -46% (95% CI: -53%, -39%). 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 32 (17%) of 191 patients treated with PRALUENT for at least 12 weeks.

At week 24, the mean percent change from baseline in LDL-C was -43% with PRALUENT and -2% with placebo, and the treatment difference between PRALUENT and placebo (LS Mean) -2% (95% CI: -3%, -1%).

Table 3: Mean Percent Change from Baseline and Difference* from Placebo in Lipid Parameters at Week 12 and Week 24 in Patients with HeFH (Studies 3 and 4 Pooled)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>LDL-C (Mean Percent Change from Baseline)</th>
<th>Total-C</th>
<th>Non-HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>PRALUENT (75 mg)</td>
<td>-43</td>
<td>-27</td>
<td>-38</td>
<td>-34</td>
</tr>
<tr>
<td>Difference from placebo (LS Mean) (95% CI)</td>
<td>-48 (-52, -44)</td>
<td>-31 (-34, -28)</td>
<td>-42 (-46, -39)</td>
<td>-36 (-39, -33)</td>
</tr>
</tbody>
</table>

* Difference is PRALUENT minus Placebo

†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.

Study 6 was a multi-center, double-blind, placebo-controlled trial that randomly assigned 109 patients to PRALUENT 75 mg Q2W and 35 patients to placebo. Patients had HeFH with a baseline LDL-C ≥160 mg/dL while taking a maximally tolerated dose of statin with or without other lipid-modifying therapy. The mean age was 51 years (range 18–80); 47% were women, 88% were Caucasian, 2% were Black, and 6% were Hispanic/Latino. Overall, 50% had clinical atherosclerotic cardiovascular disease. The average LDL-C at baseline was 198 mg/dL.

The proportion of patients who prematurely 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 percent change from baseline in LDL-C was -45% with PRALUENT and -7% with placebo, and the treatment difference between PRALUENT and placebo in mean LDL-C percent change was -38% (95% CI: -49%, -24%; p-value: <0.0001).

Study 6 was a multi-center, double-blind, placebo-controlled trial that randomly assigned 312 patients to PRALUENT 300 mg Q4W, 78 patients to PRALUENT 75 mg Q2W, and 157 patients to placebo who had hypercholesterolemia and were taking concomitant statin. The mean age was 62 years (range 21–88); 37% were women, 88% were Caucasian, 10% were Black, and 2% were Hispanic/Latino. Of these, 64% of patients had clinical atherosclerotic cardiovascular disease and 8% had HeFH. The mean LDL-C at baseline was 113 mg/dL.

The proportion of patients who prematurely 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 between PRALUENT 300 mg Q4W and placebo in mean percent change in LDL-C from baseline was 54% (97.5% CI: -61%, -48%), and the treatment difference between PRALUENT 75 mg Q2W and placebo in mean percent change in LDL-C was -44% (97.5% CI: -53%, -35%) (Figure 3).

Figure 3: Mean Percent Change from Baseline in LDL-C up to Week 12 in 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.

At week 12, if additional LDL-C lowering was required based on pre-specified LDL-C criteria, PRALUENT was adjusted to 150 mg Q2W for the remainder of the trial. The dose was adjusted to 150 mg Q2W in approximately 20% of patients treated with PRALUENT 75 mg Q2W or 300 mg Q4W for at least 12 weeks. 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 -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%).

Study 7 was a multicenter, double-blind, placebo-controlled trial that randomly assigned patients with HeFH who were undergoing LDL apheresis to PRALUENT 150 mg Q2W (N=41) or placebo (N=21). Patients were treated in combination with their usual LDL apheresis schedule for 6 weeks. The mean age was 59 years (range 27–79), 42% were women, 97% were Caucasian, 3% were Black, and 0% were Hispanic/Latino. The mean LDL-C at baseline, measured before the apheresis procedure, was 181 mg/dL. The proportion of patients who discontinued study drug prior to the 6-week endpoint was 2% among those treated with PRALUENT 150 mg Q2W and 5% among those treated with placebo. At week 6, the mean percent change from baseline in pre-apheresis LDL-C was -53% in patients in the PRALUENT group compared to 1% in patients who received placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

PRALUENT is a clear, colorless to pale yellow solution, supplied in single-dose pre-filled pens and single-dose pre-filled glass syringes. Each pre-filled pen or pre-filled syringe of PRALUENT is designed to deliver 1 mL of 75 mg/mL or 150 mg/mL solution.

PRALUENT is available in cartons containing 1 or 2 pre-filled pens and 1 or 2 pre-filled syringes.

<table>
<thead>
<tr>
<th>Pack Size</th>
<th>75 mg/mL Pre-filled Pen</th>
<th>150 mg/mL Pre-filled Pen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pack of 1 pen</td>
<td>NDC 0024-5901-01</td>
<td>NDC 0024-5902-01</td>
</tr>
<tr>
<td>Pack of 2 pens</td>
<td>NDC 0024-5901-02</td>
<td>NDC 0024-5902-02</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Pack Size</th>
<th>75 mg/mL Pre-filled Syringe</th>
<th>150 mg/mL Pre-filled Syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pack of 1 syringe</td>
<td>NDC 0024-5903-01</td>
<td>NDC 0024-5904-01</td>
</tr>
<tr>
<td>Pack of 2 syringes</td>
<td>NDC 0024-5903-02</td>
<td>NDC 0024-5904-02</td>
</tr>
</tbody>
</table>

Storage
Pharmacy
Store in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton in order to protect from light.

Patient/Caregiver
Store in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton in order to protect from light. If needed, PRALUENT may be kept at room temperature up to 77°F (25°C) for a maximum of 30 days in original carton to protect from light. Do not store above 77°F (25°C). After removal from the refrigerator, PRALUENT must be used within 30 days or discarded.

Do NOT freeze. Do NOT expose to extreme heat. Do NOT shake.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information and Instructions for Use).

Pregnancy Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to PRALUENT during pregnancy. Encourage participation in the registry [see Use in Specific Populations (8.1)].

Allergic Reactions
- Advise patients to discontinue PRALUENT and seek prompt medical attention if any signs or symptoms of serious allergic reactions occur.
- Instruct patients and caregivers to read the Patient Information and Instructions For Use (IFU) before the patient starts using PRALUENT, and each time the patient gets a refill as there may be new information they need to know.
- Provide guidance to patients and caregivers on proper subcutaneous injection technique, including aseptic technique, and how to use the pre-filled pen or pre-filled syringe correctly (see Instructions for Use leaflet). Inform patients that it may take up to 20 seconds to inject PRALUENT.
- The pre-filled pen or pre-filled syringe should be allowed to warm to room temperature for 30 to 40 minutes prior to use.
- Patients and caregivers should be cautioned that the pre-filled pen or pre-filled syringe must not be re-used and instructed in the technique of proper pen and syringe disposal in a puncture-resistant container. Do not recycle the container.

Manufactured by:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

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U.S. License # 1752

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