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)

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)

If an every-4-week dose is missed, 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.

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)

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)

The effect of PRALUENT on cardiovascular morbidity and mortality has not been determined. (1.2)

Dosage Forms and Strengths

Injection: 75 mg/mL or 150 mg/mL solution in a single-dose pre-filled pen (3)

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: 12/2018
6.4 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 2135 exposed for 6 months and 1999 exposed for more than 1 year (median treatment duration 2 years). Rates of injection site reactions versus no patients (0%) in the other 2 treatment groups.

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 Reactions</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 spasm</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 versus no patients (0%) in the other 2 treatment groups.

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) positivity in an assay may be influenced by several factors including assay methodology, sample handling, collection, concentration, and storage conditions, and the 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 ten 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) detected at least once after initiating treatment compared with 0.8% (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) detected at least once, and 0.3% (9/3033) exhibited some attenuation in efficacy. No patients treated with control developed NAb.

6.3 Postmarketing Experience

The following adverse reactions have been reported during postapproval use of PRALUENT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

• General disorders and administration site conditions

Flu-like illness

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 assessment. In animal reproduction studies, there were no effects on embryo-fetal development when rats were subcutaneously administered alirocabum during organogenesis at doses up to 12-fold the exposure at the maximum recommended human dose of 150 mg every 2 weeks. In monkeys, suppression of the humoral immune response was observed in infants when alirocabum was administered during organogenesis in pregnant monkeys at doses up to 81-fold the exposure at the maximum recommended human dose of 150 mg every 2 weeks. Additional effects on pregnancy or neonatal development were observed at doses exposures up to 81-fold the maximum recommended human dose of 150 mg every 2 weeks.

FDA’s experience with monoclonal antibodies in humans indicates that they are unlikely to cross the placenta in the first trimester; however, they are likely to cross the placenta in increasing amounts in the second and third trimester. Consider the benefits and risks of PRALUENT and possible risks to the fetus before prescribing PRALUENT to pregnant women.
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal data

In Sprague Dawley rats, no effects on embryo-fetal development were observed when alirocumab was administered at up to 75 mg/kg/day 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, based on serum AUC.

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 lowest dose tested in the monkey resulted in humoral 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 maternally-effects were observed, when alirocumab was dosed at up to 75 mg/kg/day when 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 breastfeeding 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 breastfeeding 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 binds to 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 human heavy chains, each covalently linked through a single cysteine residue to a heavy chain-derived human kappa light chain. The heavy chain 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 sterilized 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 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.

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

Absorption

After subcutaneous (SC) administration of 75 mg to 300 mg alirocumab, median times to maximum serum concentrations (tmax) were 3 hours. 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 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 and Elimination

Specific metabolisms were not conducted, because alirocumab is a protein. Metabolism includes catabolism of 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 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)].

13 NONCLINICAL TOXICOLOLGY

13.1 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 chromosomes.

There were no adverse effects on surrogate markers of fertility (e.g., estrous cyclicity, testicular volume, ejaculate volume, sperm motility, or total sperm count per ejaculate) in a 6-month chronic toxicology study in sexually-mature monkeys subcutaneously administered at 5, 15, and 75 mg/kg/week at systemic exposures up to 103-fold the 150 mg every two 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 study, compared to clinical systemic exposure following a 150 mg every two weeks subcutaneous dose on serum AUC.

13.2 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 of alirocumab on the hemodynamic response to keyhole limpet hemocyanin (KLH) after one to two months at exposures 100-fold greater than the exposure at the maximum recommended human dose of 150 mg every two weeks, based on AUC.

14 CLINICAL STUDIES

The efficacy of PRALUENT was investigated in five double-blind placebo-controlled 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 trials were conducted exclusively in patients with HeFH and all patients were receiving a maximally tolerated dose of a 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, and a modified intention-to-treat population was analyzed.

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 six double-blind, placebo-controlled, 48-week trial enrolled 574 patients on maximally tolerated dose of a 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).

Three studies used an initial dose of 75 mg every 2 weeks (Q2W) followed by criteria-based up-titration to 150 mg Q2W at week 12 for patients who did not achieve their primary LDL-C goal with 75 mg Q2W (on day 1 and week 1). On day 1 and week 1, 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.
and required additional LDL-C reduction. The mean age was 61 years (range 18–89), 38% were women, 93% were Caucasian, 3% were Black, and 5% were Hispanic/Latino. Overall, 69% were non-HFH 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 6% 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.

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</th>
<th>Total-C</th>
<th>Non-HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

Difference from placebo (LS Mean (95% CI) )

-58 (-61, -56)
-36 (-37, -34)
-50 (-52, -47)
-51 (-53, -48)

†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.

Figure 1: Mean Percent Change from Baseline in LDL-C Over 52 Weeks in Patients on Maximally Tolerated Statin Treated with PRALUENT 150 mg Q2W and Placebo Q2W (Study 1)

*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.

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. The average LDL-C was 102 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 196 (42%) of 469 patients treated with PRALUENT for at least 12 weeks. At week 24, the mean treatment difference between PRALUENT and placebo in mean LDL-C percent change from baseline was -54% (95% CI: -59%, -50%; p-value: <0.0001). The LDL-C-lowering effect was sustained to week 52. For additional results see Table 3 and Figure 2.

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</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>
</tbody>
</table>

Difference from placebo (LS Mean (95% CI) )

-48 (-52, -44)
-31 (-34, -28)
-42 (-46, -39)
-36 (-39, -33)

**Week 24 (Mean Percent Change from Baseline)**

| Placebo         | 7     | 5       | 7         | 2     |
| PRALUENT (75 mg) | -47   | -30     | -42       | -40   |

Difference from placebo (LS Mean (95% CI) )

-54 (-59, -50)
-36 (-39, -33)
-49 (-53, -45)
-42 (-45, -39)

*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.
‡Dose was up-titrated to 150 mg Q2W in 196 (42%) patients treated for at least 12 weeks.

Figure 2: Mean Percent Change from Baseline in LDL-C Over 52 Weeks in Patients with HeFH on Maximally-Tolerated Statin Treated with PRALUENT 75/150 mg Q2W and Placebo Q2W (Studies 3 and 4 Pooled)

*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.

Study 5 was a multicenter, double-blind, placebo-controlled trial that randomly assigned 72 patients to PRALUENT 150 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 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 -43% with PRALUENT and -7% with placebo, and the treatment difference between PRALUENT and placebo in mean LDL-C percent change was -36% (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 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 157 patients to placebo who had hypercholesterolemia and were taking concomitant statin. The mean age was 49 years (range 25–79), 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 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.

Manufactured by:

sandofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY
U.S. License # 1752
Marketed by: sandofi-aventis U.S. LLC (Bridgewater, NJ 08807) and Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591)
PRALUENT is a registered trademark of Sanofi
©2018 Regeneron Pharmaceuticals, Inc. / sandofi-aventis U.S. LLC
What should I tell my healthcare provider before using PRALUENT?
Before you start using PRALUENT, tell your healthcare provider about all your medical conditions, including allergies, and if you:
- are pregnant or plan to become pregnant. It is not known if PRALUENT will harm your unborn baby. Tell your healthcare provider if you become pregnant while taking PRALUENT.
- are breastfeeding. PRALUENT and its active ingredient, alirocumab, can be detected in breast milk. It is not known if alirocumab or PRALUENT will harm your baby or affect breast milk supply. You and your healthcare provider should decide if you will take PRALUENT or breastfeed. You should not do both without talking to your healthcare provider first.
- tell your healthcare provider or pharmacist about any prescription and over-the-counter medicines you are taking or plan to take, including natural or herbal remedies.

Pregnancy Registry. There is a pregnancy registry for women who take PRALUENT during pregnancy. The purpose of this registry is to collect information about your health and your baby's health. You can talk to your healthcare provider or contact 1-877-311-8972 or go to https://mothertobaby.org/ongoing-study/praluent/ to enroll in this registry or get more information.

What are the ingredients in PRALUENT?
- Active ingredient: alirocumab
- Inactive ingredients: histidine, polysorbate 20, sucrose, and water for injection.

How should I use PRALUENT?
- See the detailed “Instructions for Use” that comes with this patient information about the right way to prepare and give your PRALUENT injections.
- Use PRALUENT exactly as your healthcare provider tells you to use it.
- 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 dosage that is best for you.
- If your healthcare provider decides that you or a caregiver can give the injections of PRALUENT, you or your caregiver should receive training on the right way to prepare and administer PRALUENT. Do not try to inject PRALUENT until you have been shown the right way by your healthcare provider or nurse.
- PRALUENT is injected under the skin (subcutaneously) every 2 weeks or every 4 weeks (monthly).
- If your healthcare provider prescribes you the monthly dose, you will give yourself 2 separate injections in a row, using a different syringe or pen for each injection and two different injection sites.
- Do not inject PRALUENT together with other injectable medicines at the same injection site.
- Always check the label of your pen or syringe to make sure you have the correct medicine and the correct dose of PRALUENT before each injection.
- If you forget to use PRALUENT or are not able to take the dose at your regular time, inject your missed dose as soon as you remember, within 7 days. Then, if you inject every 2 weeks take your next dose in 2 weeks from the day you missed your dose or if you inject every 4 weeks take your next dose in 4 weeks from the day you missed your dose. This will put you back on your original schedule.
- If you missed a dose by more than 7 days and you inject every 2 weeks wait until your next scheduled dose to re-start PRALUENT or if you inject every 4 weeks start a new schedule from the time you remember to take your dose. If you are not sure when to re-start PRALUENT, ask your healthcare provider or pharmacist.
- If you use more PRALUENT than you should, talk to your healthcare provider or pharmacist.
- Do not stop using PRALUENT without talking with your healthcare provider. If you stop using PRALUENT, your cholesterol levels can increase.

What are the possible side effects of PRALUENT?
PRALUENT can cause serious side effects, including:
- allergic reactions. PRALUENT may cause allergic reactions that can be severe and require treatment in a hospital. Call your healthcare provider or go to the nearest hospital emergency room right away if you have any symptoms of an allergic reaction including a severe rash, redness, severe itching, a swollen face, or trouble breathing.
- Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of PRALUENT. Ask your healthcare provider or pharmacist for more information. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of PRALUENT.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use PRALUENT for a condition for which it was not prescribed. Do not give PRALUENT to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information summarizes the most important information about PRALUENT. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about PRALUENT that is written for health professionals.

For more information about PRALUENT, go to www.PRALUENT.com or call 1-844-PRALUENT (1-844-772-5836).

What are the ingredients in PRALUENT?
- Active ingredient: alirocumab
- Inactive ingredients: histidine, polysorbate 20, sucrose, and water for injection.

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This Patient Information has been approved by the U.S. Food and Drug Administration.
Revised: August 2018

ALI-FPLR-SL-MAR19a Rx Only