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.

Common Adverse Reactions

The data in Table 1 are derived from 9 primary hyperlipidemia 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 of 65 weeks). The mean age of the population was 59 years, 40% of the population were women, 90% were Caucasian, 4% were Black or African American, and 3% were Asian.

Adverse reactions reported in at least 2% of PRALUENT-treated patients, and more frequently than in placebo-treated patients, are shown in Table 1.

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

Adverse Reactions	**Placebo** (N=1276)	**PRALUENT**[a] (N=2476)
Nasopharyngitis	11.1%	11.3%
Injection site reactions[b]	5.1%	7.2%
Influenza	4.6%	5.7%
Urinary tract infection	4.6%	4.8%
Diarrhea	4.4%	4.7%
Bronchitis	3.8%	4.3%
Myalgia	3.4%	4.2%
Muscle spasms	2.4%	3.1%
Sinusitis	2.7%	3.0%
Cough	2.3%	2.5%
Contusion	1.3%	2.1%
Musculoskeletal pain	1.6%	2.1%

[a] 75 mg every 2 weeks and 150 mg every 2 weeks combined
[b] 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%).

In an analysis of ezetimibe-controlled trials in which 864 patients were exposed to PRALUENT for a median of 27 weeks and 618 patients were exposed to ezetimibe for a median of 24 weeks, the types and frequencies of common adverse reactions were similar to those listed above.

In a cardiovascular outcomes trial in which 9451 patients were exposed to PRALUENT for a median of 31 months and 9443 patients were exposed to placebo for a median of 32 months, common adverse reactions (greater than 5% of patients treated with PRALUENT and occurring more frequently than placebo) included non-cardiac chest pain (7.0% PRALUENT, 6.8% placebo), nasopharyngitis (6.0% PRALUENT, 5.6% placebo), and myalgia (5.6% PRALUENT, 5.3% placebo).

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.

In a cardiovascular outcomes trial, local injection site reactions were reported in 3.8% of patients treated with PRALUENT versus 2.1% patients treated with placebo, and led to permanent discontinuation in 26 patients (0.3%) versus 3 patients (<0.1%), respectively.

Allergic Reactions

Allergic reactions were reported more frequently in patients treated with PRALUENT than in those treated with placebo (8.6% 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)*].

Liver Enzyme Abnormalities

In the primary hyperlipidemia trials, liver-related 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 primary hyperlipidemia trials using an every 2 week or every 4 week dosing interval, 914 PRALUENT-treated patients had two consecutive calculated LDL-C values <25 mg/dL, and 335 had two consecutive calculated 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-altering therapy (e.g., maximally tolerated statins) were not made in response to low LDL-C values in these trials, and PRALUENT dosing was not modified or interrupted on this basis.

In a cardiovascular outcomes trial, 4305 PRALUENT-treated patients had two consecutive calculated LDL-C values <25 mg/dL, and 782 had two consecutive calculated LDL-C values <15 mg/dL. Because PRALUENT dosing was decreased or discontinued in the event of two consecutive LDL-C values <15 mg/dL in this trial, the effects of prolonged very low LDL-C with PRALUENT are unknown.

In published genetic studies as well as clinical and observational trials with lipid lowering therapies, an increased risk of new onset of diabetes has been associated with lower levels of LDL-C.

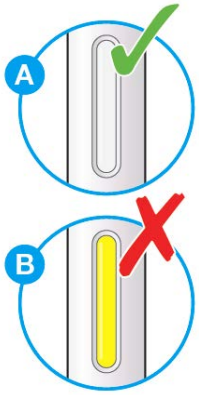
6.2 Immunogenicity

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, 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 cardiovascular outcomes trial, 5.5% (504/9091) of patients treated with PRALUENT 75 mg and/or 150 mg every 2 weeks (Q2W) had anti-drug antibodies (ADA) detected after initiating treatment compared with 1.6% (149/9097) of patients treated with placebo. Persistent ADA responses, defined as at least 2 consecutive post-baseline samples with positive ADA separated by at least a 16-week period, were observed in 0.7% of patients treated with PRALUENT and 0.4% of patients treated with placebo. Neutralizing antibody (NAb) responses were observed in 0.5% of patients treated with PRALUENT and in <0.1% of patients treated with placebo. Efficacy based on reductions in LDL-C was mostly similar in patients with or without ADA.

A2: Look at the window.

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



A3: Let the pen warm up at room temperature for 30 to 40 minutes.

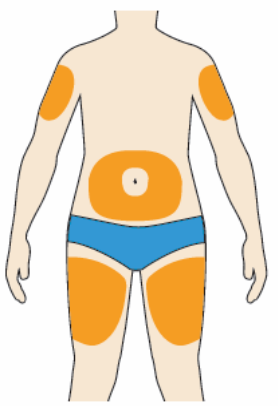
- This is important for administering the entire dose and helps minimize discomfort.
- Take PRALUENT out of the refrigerator to warm up before using.
- **Do not** heat the pen, let it warm up on its own.
- **Do not** put the pen back in the refrigerator.

A4: 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):
  - thighs
  - stomach (except for the 2 inch area around your navel)
  - upper arms
- You can stand or sit to give yourself an injection.

Important:

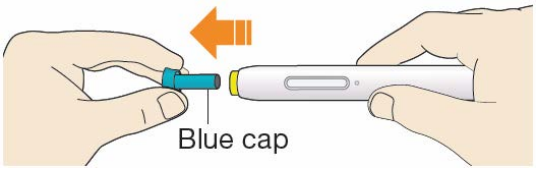
- Change (rotate) your injection site each time you give yourself an injection. If you need to use the same injection site, make sure it is not the same spot on the site you used last time.
- **Do not** inject into areas where the skin is injured, tender, hard, red, or hot. **Do not** inject PRALUENT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



Step B: How to give your injection

B1: After completing all steps in "Step A: Getting ready for your 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.

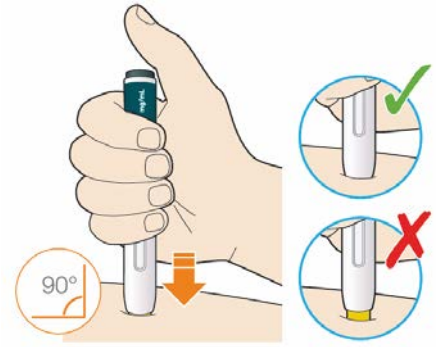


B2: Hold the PRALUENT pen like this.

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

B3: 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.



B4: Push and immediately release the gray button with your thumb.

- You will hear a click. Your injection has now started.
- The window will start to turn yellow.

B5: Keep holding the pen against your skin after releasing the button.

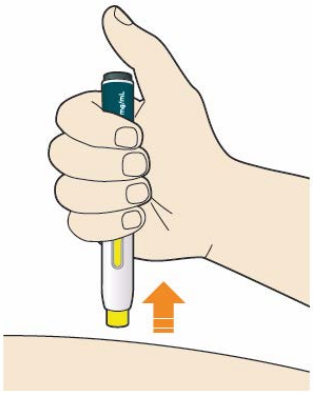
- The injection may take up to 20 seconds.
- The time required for injection to give the entire dose may be longer than for other injectable medicines.

B6: 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 1-844-772-5836 for help. **Do not** give yourself a second dose without speaking to your healthcare provider.

B7: 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.



B8: Discard pen and cap.

- **Do not** put the blue cap back on.
- Throw away pen and cap in a puncture-resistant container immediately after they have been used.

Disposing of used pens:

- Put your used pens in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) pens and caps in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:

    - made of a heavy-duty plastic,
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
    - upright and stable during use,
    - leak-resistant, and
    - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

Keep PRALUENT and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

REGENERON SANOFI

Manufactured by:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY
U.S. License # 1752

Marketed by: sanofi-aventis U.S. LLC (Bridgewater, NJ 08807)

and Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591)

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