CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125559Orig1s000

<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PRALUENT safely and effectively. See full prescribing information for PRALUENT.

PRALUENT™ (alirocumab) injection, for subcutaneous use
Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------
PRALUENT is a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor antibody indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-cholesterol (LDL-C). (1.1)

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

----------DOSAGE AND ADMINISTRATION----------
The recommended starting dose for PRALUENT is 75 mg administered subcutaneously once every 2 weeks, since the majority of patients achieve sufficient LDL-C reduction with this dosage. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks. (2.1)

Measure LDL-C levels within 4 to 8 weeks of initiating or titrating PRALUENT, to assess response and adjust the dose, if needed. (2.1)

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

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

----------WARNINGS AND PRECAUTIONS----------
- 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. (5.1)

----------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: 7/2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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 or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.

1.2 Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended starting dose of PRALUENT is 75 mg administered subcutaneously once every 2 weeks, since the majority of patients achieve sufficient LDL-C reduction with this dosage. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks.

Measure LDL-C levels within 4 to 8 weeks of initiating or titrating PRALUENT to assess response and adjust the dose, if needed.

If a 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 wait until the next dose on the original schedule.

2.2 Important Administration Instructions

- Provide proper training to patients and/or caregivers on the preparation and administration of PRALUENT prior to use according to the Instructions for Use. Instruct patients and/or caregivers to read and follow the Instructions for Use each time they use PRALUENT.
- Allow PRALUENT to warm to room temperature for 30 to 40 minutes prior to use. Use PRALUENT as soon as possible after it has warmed up. Do NOT use PRALUENT if it has been at room temperature [77°F (25°C)] for 24 hours or longer.
- 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.
- Follow aseptic injection technique every time PRALUENT is administered.
- Administer PRALUENT by subcutaneous injection into the thigh, abdomen, or upper arm using a single-dose pre-filled pen or single-dose pre-filled syringe.
- Rotate the injection site with each injection.

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- Do NOT inject PRALUENT 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.

3 DOSAGE 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.

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The safety of PRALUENT was evaluated in 9 placebo-controlled trials that included 2476 patients treated with PRALUENT, 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 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.

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%).

Local Injection Site Reactions

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.

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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)*].

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

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 a pool of both placebo- and active-controlled clinical trials, 796 PRALUENT-treated patients had two consecutive calculated LDL-C values <25 mg/dL, and 288 had two consecutive calculated LDL-C values <15 mg/dL. Changes to background lipid-altering 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. In a pool of ten placebo- and active-controlled trials, 4.8% of patients treated with PRALUENT had anti-drug antibodies (ADA) newly detected after initiating treatment as compared with 0.6% of patients treated with control.

Patients who developed ADA had a higher incidence of injection site reactions compared with patients who did not develop ADA (10.2% vs 5.9%).

A total of 1.2% of patients treated with PRALUENT developed neutralizing antibodies (NAb) on at least one occasion as compared with no patients treated with control, and 0.3% of patients both tested positive for NAb and exhibited transient or prolonged loss of efficacy. 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

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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 PRALUENT with the incidence of antibodies to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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. No additional effects on pregnancy or neonatal/infant development were observed at dose exposures up to 81-fold the maximum recommended human dose of 150 mg every two weeks. Measurable alirocumab serum concentrations were observed in the infant monkeys at birth at comparable levels to maternal serum, indicating that alirocumab, like other IgG antibodies, crosses the placental barrier. 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 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, 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- 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 maternal effects were observed, when

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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 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 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 (IgG1 isotype) 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 human heavy 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.

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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 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 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 quantitation.

12.3 Pharmacokinetics

Absorption

After subcutaneous (SC) administration of 75 mg to 150 mg alirocumab, median times to maximum serum concentrations (t_{max}) 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- to 2.7-fold increase in total alirocumab concentrations for a 2-fold increase in dose. Steady state was reached after 2 to 3 doses with an accumulation ratio 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 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

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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)*].

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.

Hepatic Impairment

Following administration of a single 75 mg SC dose, alirocumab pharmacokinetic profiles in subjects with mild and moderate hepatic impairment were similar to those in subjects with normal hepatic function.

No data are available in patients with severe hepatic impairment.

Drug-Drug Interactions

The median apparent half-life of alirocumab is reduced to 12 days when administered with a statin; however, this difference is not clinically meaningful and does not impact dosing recommendations.

13 NONCLINICAL TOXICOLOGY

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

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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 studies, compared to clinical systemic exposure following a 150 mg every two weeks dose, based 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 PRALUENT on the humoral immune 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. 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 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-titration 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.

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 statins with or without other lipid-modifying therapy, 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-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.

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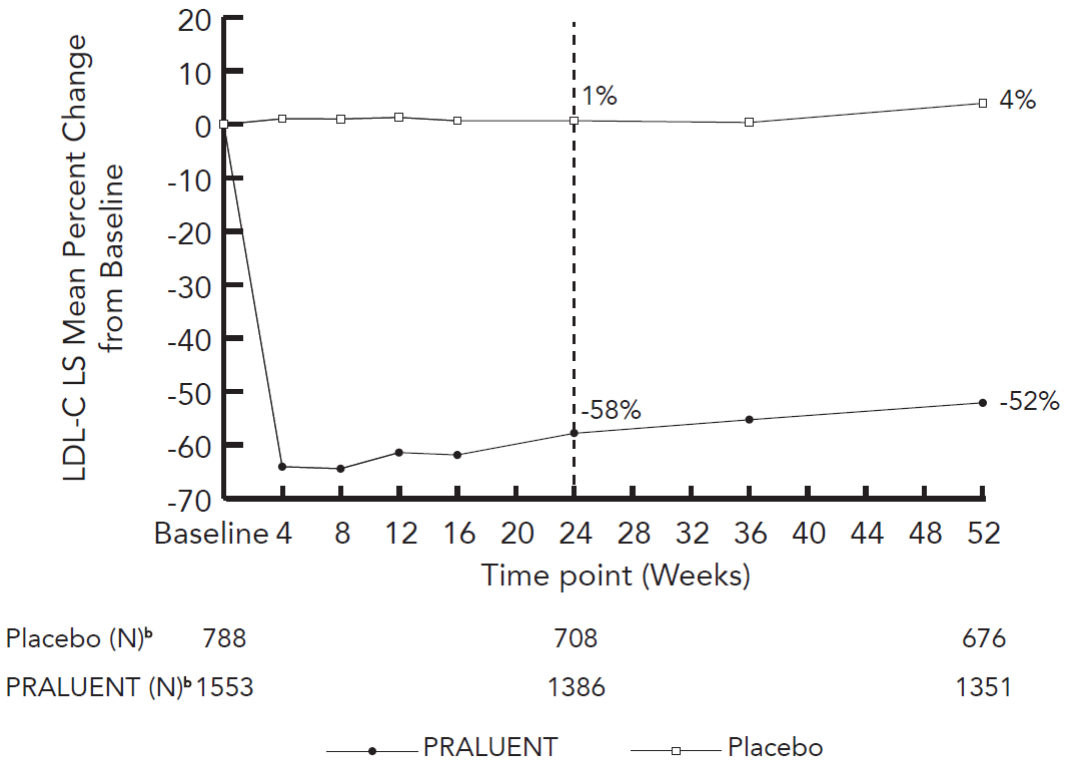
Table 2 Mean Percent Change from Baseline and Difference[a] from Placebo in Lipid Parameters at Week 24 in Study 1[b]

Treatment Group	LDL-C	Total-C	Non-HDL-C	Apo B
Week 24 (Mean Percent Change from Baseline)				
Placebo	1	0	1	1
PRALUENT (150 mg)	-58	-36	-49	-50
Difference from placebo (LS Mean) (95% CI)	-58 (-61, -56)	-36 (-37, -34)	-50 (-52, -47)	-51 (-53, -48)

[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.

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)[a]



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

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Study 2 was a multicenter, double-blind, placebo-controlled trial that randomly assigned 209 patients to PRALUENT and 107 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.

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 75mg 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. At week 24, the mean percent change from baseline in LDL-C was -44% with PRALUENT and -2% with placebo, and the treatment difference between PRALUENT and placebo in mean LDL-C percent change was -43% (95% CI: -50%, -35%; p-value: <0.0001). The dose was up-titrated to 150 mg Q2W in 32 (17%) of 191 patients treated with PRALUENT for at least 12 weeks.

Studies 3 and 4 were multicenter, double-blind, placebo-controlled trials that, combined, randomly assigned 490 patients to PRALUENT and 245 to placebo. The trials were similar with regard to both design and eligibility criteria. All patients had HeFH, were taking a maximally tolerated dose of statin with or without other lipid-modifying therapy, and required additional LDL-C reduction. The mean age was 52 years (range 20-87), 45% were women, 94% were Caucasian, 1% were Black, and 3% were Hispanic/Latino. Overall, 45% of these patients with HeFH also had clinical atherosclerotic cardiovascular disease. The average LDL-C at baseline was 141 mg/dL.

Considering both trials together, the proportion of patients who prematurely discontinued study drug prior to the 24-week endpoint was 6% among those treated with PRALUENT and 4% among those treated with placebo.

At week 12, the treatment difference between PRALUENT 75 mg Q2W and placebo in mean LDL-C percent change was -48% (95% CI: -52%, -44%).

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 trials. 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 dose was up-titrated to 150 mg Q2W in 196 (42%) of 469 patients treated with PRALUENT for at least 12 weeks. The LDL-C-lowering effect was sustained to week 52.

For additional results see Table 3 and Figure 2.

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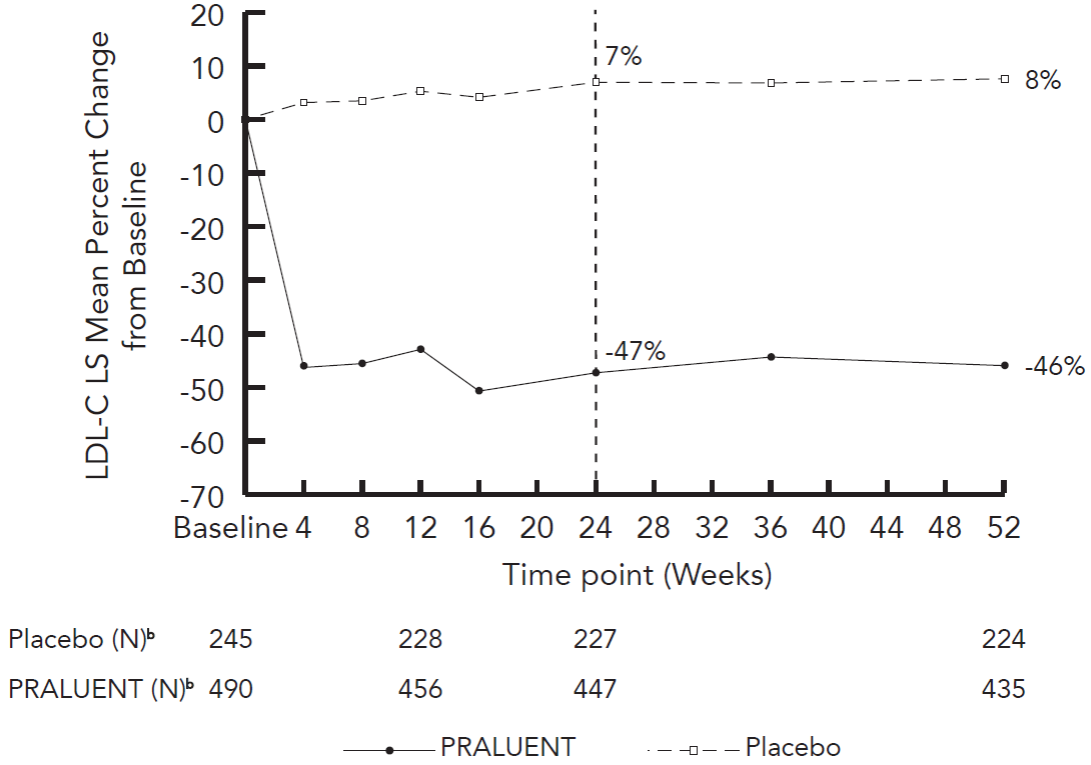
Table 3 Mean Percent Change from Baseline and Difference[a] from Placebo in Lipid Parameters at Week 12 and Week 24 in Patients with HeFH (Studies 3 and 4 Pooled)[b]

Treatment Group	LDL-C	Total-C	Non-HDL-C	Apo B
Week 12 (Mean Percent Change from Baseline)				
Placebo	5	4	5	2
PRALUENT (75 mg)	-43	-27	-38	-34
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/up150 mg[c])	-47	-30	-42	-40
Difference from placebo (LS Mean) (95% CI)	-54 (-59, -50)	-36 (-39, -33)	-49 (-53, -45)	-42 (-45, -39)

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

Reference ID: 3797282

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)[a]



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

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).

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.

Reference ID: 3797282

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

Pack Size	**75 mg/mL Pre-Filled Pen**	**150 mg/mL Pre-Filled Pen**
Pack of 1 pen	NDC 0024-5901-01	NDC 0024-5902-01
Pack of 2 pens	NDC 0024-5901-02	NDC 0024-5902-02

Pack Size	**75 mg/mL Pre-Filled Syringe**	**150 mg/mL Pre-Filled Syringe**
Pack of 1 syringe	NDC 0024-5903-01	NDC 0024-5904-01
Pack of 2 syringes	NDC 0024-5903-02	NDC 0024-5904-02

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

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).

Allergic Reactions

- Advise patients to discontinue PRALUENT and seek prompt medical attention if any signs or symptoms of serious allergic reactions occur.

Instructions for Administration

- 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. PRALUENT should be used as soon as possible after it has warmed up. Time out of refrigeration should not exceed 24 hours at 77°F (25°C).
- 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.

REGENERON SANOFI

Manufactured by:

Reference ID: 3797282

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807,
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Marketed by sanofi-aventis U.S. LLC, (Bridgewater, NJ 08807)
and Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591)
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Issue Date: July 2015

Reference ID: 3797282

Patient Information
PRALUENT™ (PRAHL-u-ent)
(alirocumab)
Injection, for Subcutaneous Injection

What is PRALUENT?

PRALUENT is an injectable prescription medicine called a PCSK9 inhibitor. PRALUENT is used along with diet and maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia (an inherited condition that causes high levels of LDL) or atherosclerotic heart problems, who need additional lowering of LDL cholesterol.

The effect of PRALUENT on heart problems such as heart attacks, stroke, or death is not known.

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

Who should not use PRALUENT?

Do not use PRALUENT if you are allergic to alirocumab or to any of the ingredients in PRALUENT. See the end of this leaflet for a complete list of ingredients in PRALUENT.

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 or plan to breastfeed. 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.

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 dose 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 given as an injection under the skin (subcutaneously) 1 time every 2 weeks.
- **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 of your missed dose. Then, take your next dose 2 weeks from the day you missed your dose. This will put you back on your original schedule. If the missed dose is not given within 7 days, wait until your next scheduled dose to re-start PRALUENT. This will keep you on your original schedule. 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.

The most common side effects of PRALUENT include: redness, itching, swelling, or pain/tenderness at the injection site, symptoms of the common cold, and flu or flu-like symptoms.

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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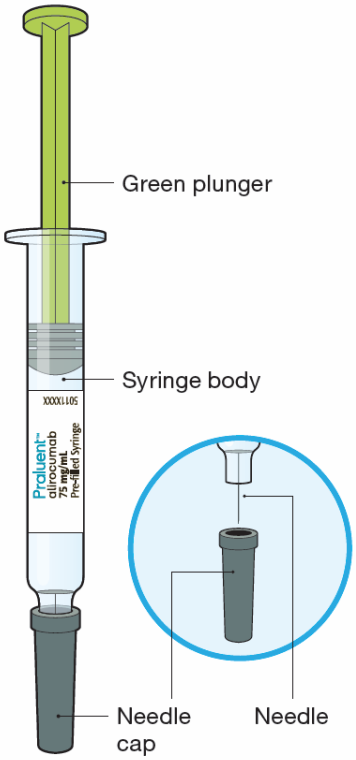
Reference ID: 3797282
This Patient Information has been approved by the U.S. Food and Drug Administration. Issue Date: July 2015

Instructions For Use
PRALUENT™ (PRAHL-u-ent)
(alirocumab)
Injection, for Subcutaneous Injection
Single-Dose Pre-Filled Syringe (75 mg/mL)

Important Information	
• The device is a single-dose pre-filled syringe. It contains 75 mg of PRALUENT (alirocumab) in 1 mL. • The PRALUENT syringe contains medicine prescribed by your healthcare provider. • The medicine is injected under your skin and can be given by yourself or someone else (caregiver). • It is important that you do not try to give yourself or someone else the injection unless you have received training from your healthcare provider. • This syringe can only be used for 1 single injection, and must be discarded after use.	• Read all of the instructions carefully before using the PRALUENT syringe. • Follow these instructions every time you use a PRALUENT syringe. • **Do not** touch the needle. • **Do not** use the syringe if it has been dropped or damaged. • **Do not** use the syringe if the gray needle cap is missing or not securely attached. • **Do not** re-use a syringe.
Storage of PRALUENT • Store unused syringes in the refrigerator between 36°F to 46°F (2°C to 8°C) in the outer carton to protect from light. • **Do not** freeze. • **Do not** expose the syringe to extreme heat or direct sunlight. • **Do not** shake. • PRALUENT should be allowed to warm to room temperature 30 to 40 minutes before use. **Do not** keep PRALUENT at room temperature for more than 24 hours. • Keep the PRALUENT syringes and all medicines out of the reach of children.	

Keep this leaflet. If you have questions, ask your healthcare provider or call 1-844-PRALUENT (1-844-772-5836).

The parts of the PRALUENT syringe are shown in this picture.



Step A: Getting ready for your injection

Before you start you will need:

- the PRALUENT syringe
- 1 alcohol wipe
- 1 cotton ball or gauze
- a puncture-resistant container (see Step B6)

A1. Before you start.

- Take the syringe out of the packaging by holding the syringe body.
- Check the expiration date: **do not** use if this date has passed.

A2. 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 liquid is clear, colorless to pale yellow and free from particles .
- Check that the syringe is not open or damaged.
- **Do not** use this medicine if the solution is discolored or cloudy, or if it contains visible flakes or particles.

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

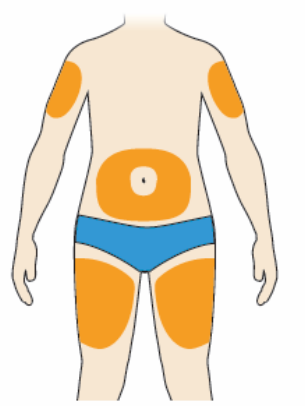
- This is important for administering the entire dose and helps minimize discomfort.
- Take PRALUENT out of the refrigerator to warm up before using.
- **Do not** heat the syringe, let it warm up on its own.
- Use the syringe as soon as possible after it has warmed up.
- **Do not** put the syringe back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

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:

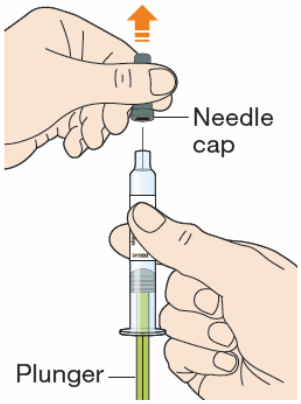
- Change (rotate) your injection site each time you give yourself an injection. If you need to use the same injection site, make sure it is not the same spot on the site you used last time.
- **Do not** inject into areas where the skin is injured, tender, hard, red, or hot. **Do not** inject PRALUENT 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 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** try to remove any air bubbles in the syringe before the injection.
- **Do not** put the gray cap back on the needle.

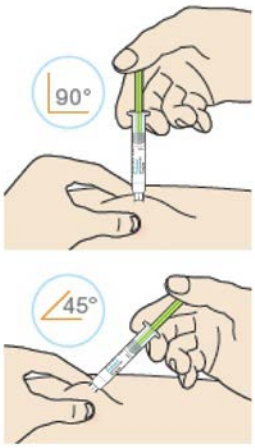


B2: If needed pinch the skin.

- Use your thumb and first finger to pinch a fold of skin at the injection site.
- Hold the skin like this during the entire injection.

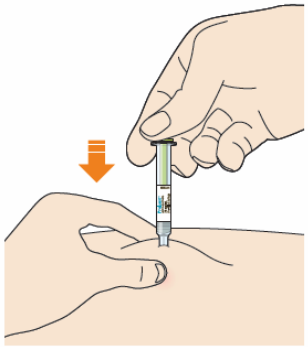
B3: Insert the needle into the fold of skin with a quick dart-like motion.

- Inject the medicine at a 90° angle if you can pinch 2 inches of skin.
- Inject the medicine at a 45° angle if you can only pinch 1 inch of skin.



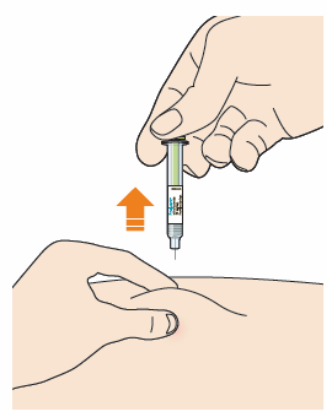
B4: Push the plunger down.

- Inject all of the medicine by slowly and steadily pushing down the plunger.
- You may have to push harder on the plunger than for other injectable medicines.



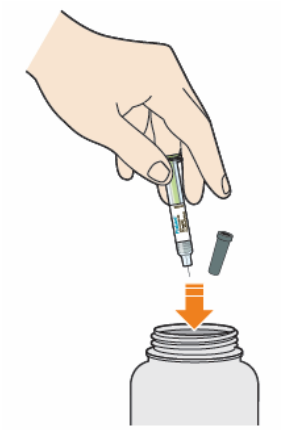
B5: Before you remove the needle check the syringe is empty.

- The time required for injection to give the entire dose may be longer than for other injectable medicines.
- **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.



B6: Discard syringe and cap.

- **Do not** put the gray needle cap back on.
- **Do no**t re-use the syringe.
- Throw away syringe and cap in a puncture-resistant container immediately after they have been used.



Disposing of used prefilled syringes and needles:

- Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes 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.

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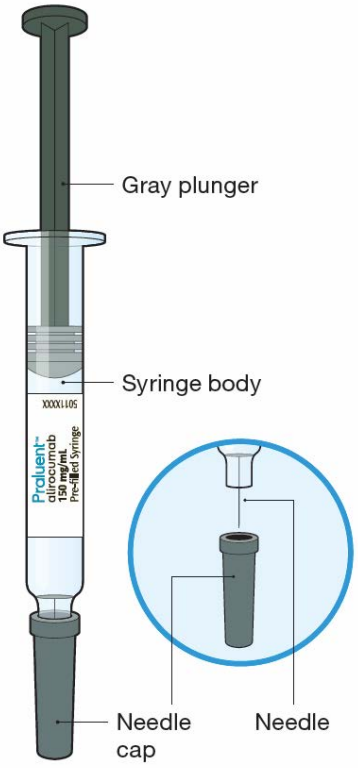
Issue Date: July 2015

Instructions For Use
PRALUENT™ (PRAHL-u-ent)
(alirocumab)
Injection, for Subcutaneous Injection
Single-Dose Pre-Filled Syringe (150 mg/mL)

Important Information	
• The device is a single-dose pre-filled syringe. It contains 150 mg of PRALUENT (alirocumab) in 1 mL. • The PRALUENT syringe contains medicine prescribed by your healthcare provider. • The medicine is injected under your skin and can be given by yourself or someone else (caregiver). • It is important that you do not try to give yourself or someone else the injection unless you have received training from your healthcare provider. • This syringe can only be used for 1 single injection, and must be discarded after use.	• Read all of the instructions carefully before using the PRALUENT syringe. • Follow these instructions every time you use a PRALUENT syringe. • **Do not** touch the needle. • **Do not** use the syringe if it has been dropped or damaged. • **Do not** use the syringe if the gray needle cap is missing or not securely attached. • **Do not** re-use a syringe.
Storage of PRALUENT • Store unused syringes in the refrigerator between 36°F to 46°F (2°C to 8°C) in the outer carton to protect from light. • **Do not** freeze. • **Do not** expose the syringe to extreme heat or direct sunlight. • **Do not** shake. • PRALUENT should be allowed to warm to room temperature 30 to 40 minutes before use. **Do not** keep PRALUENT at room temperature for more than 24 hours. • Keep the PRALUENT syringes and all medicines out of the reach of children.	

Keep this leaflet. If you have questions, ask your healthcare provider or call 1-844-PRALUENT (1-844-772-5836).

The parts of the PRALUENT syringe are shown in this picture.



Step A: Getting ready for your injection

Before you start you will need:

- the PRALUENT syringe
- 1 alcohol wipe
- 1 cotton ball or gauze
- a puncture-resistant container (see Step B6)

A1. Before you start.

- Take the syringe out of the packaging by holding the syringe body.
- Check the expiration date: **do not** use if this date has passed.

A2. 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 liquid is clear, colorless to pale yellow and free from particles.
- Check that the syringe is not open or damaged.
- **Do not** use this medicine if the solution is discolored or cloudy, or if it contains visible flakes or particles.

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

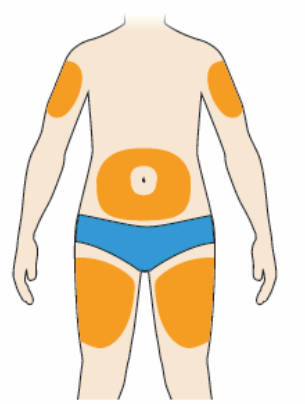
- This is important for administering the entire dose and helps minimize discomfort.
- Take PRALUENT out of the refrigerator to warm up before using.
- **Do not** heat the syringe, let it warm up on its own.
- Use the syringe as soon as possible after it has warmed up.
- **Do not** put the syringe back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

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:

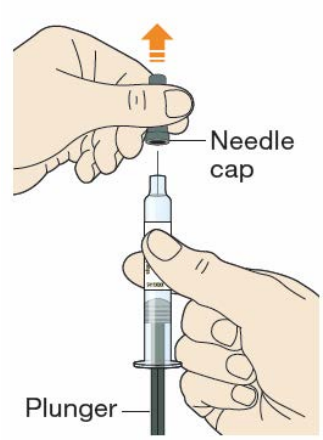
- Change (rotate) your injection site each time you give yourself an injection. If you need to use the same injection site, make sure it is not the same spot on the site you used last time.
- **Do not** inject into areas where the skin is injured, tender, hard, red, or hot. **Do not** inject PRALUENT 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 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** try to remove any air bubbles in the syringe before the injection.
- **Do not** put the gray cap back on the needle.

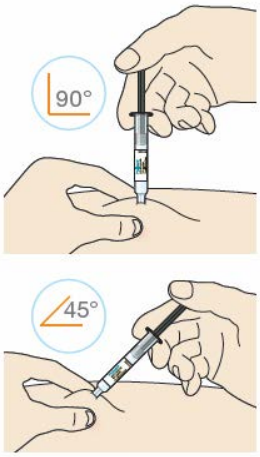


B2: If needed pinch the skin.

- Use your thumb and first finger to pinch a fold of skin at the injection site.
- Hold the skin like this during the entire injection.

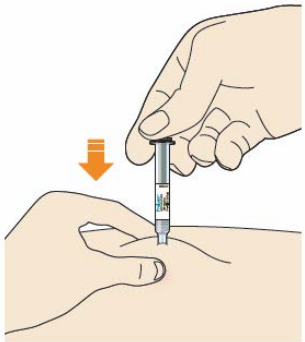
B3: Insert the needle into the fold of skin with a quick dart-like motion.

- Inject the medicine at a 90° angle if you can pinch 2 inches of skin.
- Inject the medicine at a 45° angle if you can only pinch 1 inch of skin.



B4: Push the plunger down.

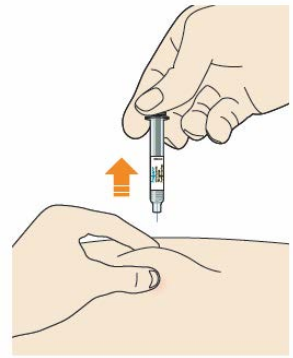
- Inject all of the medicine by slowly and steadily pushing down the plunger.
- You may have to push harder on the plunger than for other injectable medicines.



B5: Before you remove the needle check the syringe is empty.

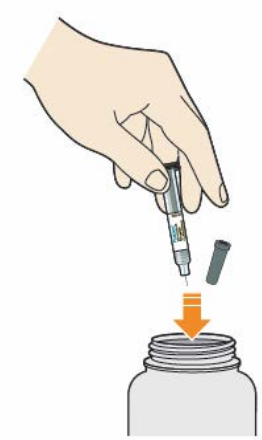
- The time required for injection to give the entire dose may be longer than for other injectable medicines.
- **Do not** remove the syringe until it is completely empty.
- Pull the needle out of the skin at the same angle as it was inserted.

- **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.



B6: Discard syringe and cap.

- **Do not** put the gray needle cap back on.
- **Do not** re-use the syringe.
- Throw away syringe and cap in a puncture-resistant container immediately after they have been used.



Disposing of used prefilled syringes and needles:

- Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes 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.

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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)

PRALUENT is a trademark of Sanofi

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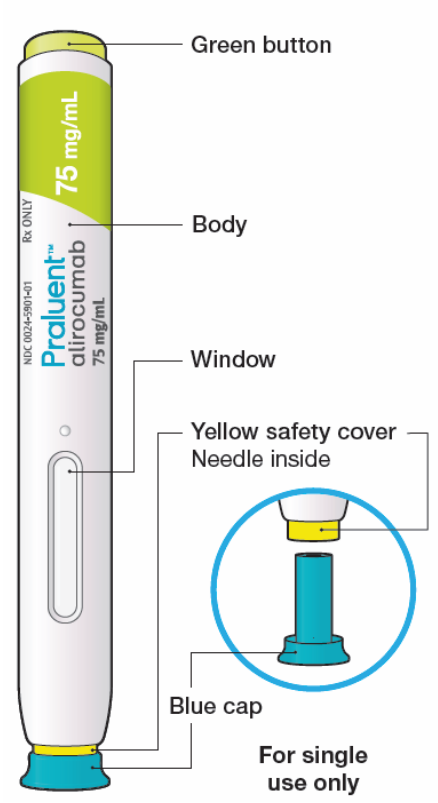
Issue Date: July 2015

Instructions For Use
PRALUENT™ (PRAHL-u-ent)
(alirocumab)
Injection, for Subcutaneous Injection
Single-Dose Pre-Filled Pen (75 mg/mL)

Important Information	
• The device is a single-dose disposable pen. It contains 75 mg of PRALUENT (alirocumab) in 1 mL. • The PRALUENT pen contains medicine prescribed by your healthcare provider. • The medicine is injected under your skin and can be given by yourself or someone else (caregiver). • It is important that you do not try to give yourself or someone else the injection unless you have received training from your healthcare provider. • This pen can only be used for 1 single injection, and must be discarded after use.	• Read all of the instructions carefully before using the PRALUENT pen. • Follow these instructions every time you use a PRALUENT pen. • **Do not** touch the yellow safety cover. • **Do not** use the pen if it has been dropped or damaged. • **Do not** use the pen if the blue cap is missing or not securely attached. • **Do not** re-use a pen.
Storage of PRALUENT • Store unused pen in the refrigerator between 36°F to 46°F (2°C to 8°C) in the outer carton to protect from light. • **Do not** freeze. • **Do not** expose the pen to extreme heat or direct sunlight. • **Do not** shake. • PRALUENT should be allowed to warm to room temperature for 30 to 40 minutes before use. **Do not** keep PRALUENT at room temperature for more than 24 hours. • Keep the PRALUENT pens and all medicines out of the reach of children.	

Keep this leaflet. If you have questions, ask your healthcare provider or call 1-844-PRALUENT (1-844-772-5836).

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



Step A: Getting ready for your injection

Before you start you will need:

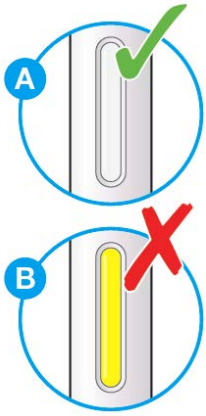
- the PRALUENT pen
- 1 alcohol wipe
- 1 cotton ball or gauze
- a puncture-resistant container (see Step B8)

A1. Look at the label on the pen.

- Check that you have the correct product and the correct dose.
- Check the expiration date: **do not** use if this date has passed.

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.
- Use the pen as soon as possible after it has warmed up.
- **Do not** put the pen back in the refrigerator.

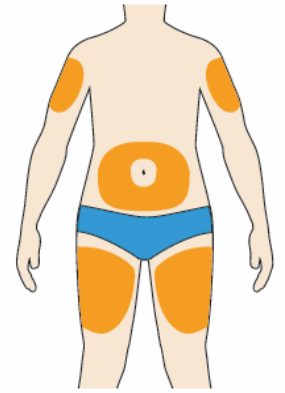
A4. Prepare the injection site.

- 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:

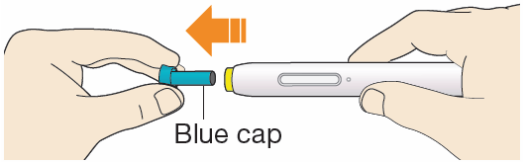
- Change (rotate) your injection site each time you give yourself an injection. If you need to use the same injection area, make sure it is not the same spot on the site you used last time.
- **Do not** inject into areas where the skin is injured, tender, hard, red, or hot. **Do not** inject PRALUENT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



Step B: How to give your injection

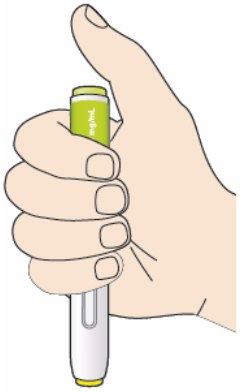
B1: **After completing all steps in "Step A: Getting ready for your injection", pull off the blue cap.**

- **Do not** pull off the cap until you are ready to inject.
- **Do not** put the blue cap back on.



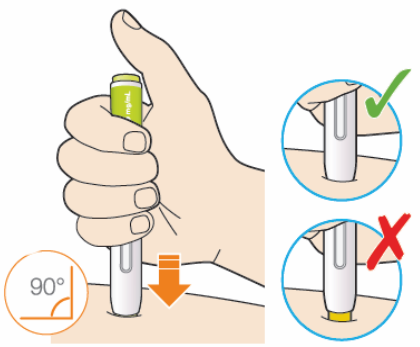
B2: Hold the PRALUENT pen like this.

- **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 green 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.

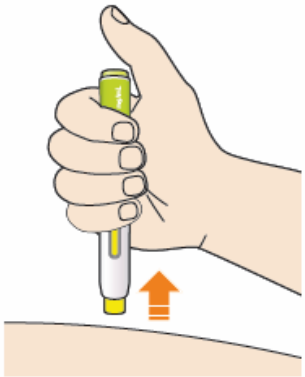
B6: Check the window has turned yellow, before removing the pen.

- **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

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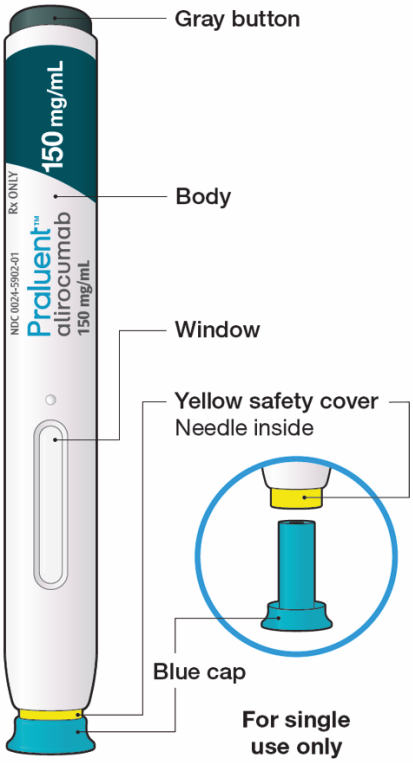
Issue Date: July 2015

Instructions For Use
PRALUENT™ (PRAHL-u-ent)
(alirocumab)
Injection, for Subcutaneous Injection
Single-Dose Pre-Filled Pen (150 mg/mL)

Important Information	
• The device is a single-dose disposable pen. It contains 150 mg of PRALUENT (alirocumab) in 1 mL. • The PRALUENT pen contains medicine prescribed by your healthcare provider. • The medicine is injected under your skin and can be given by yourself or someone else (caregiver). • It is important that you do not try to give yourself or someone else the injection unless you have received training from your healthcare provider. • This pen can only be used for 1 single injection, and must be discarded after use.	• Read all of the instructions carefully before using the PRALUENT pen. • Follow these instructions every time you use a PRALUENT pen. • **Do not** touch the yellow safety cover. • **Do not** use the pen if it has been dropped or damaged. • **Do not** use the pen if the blue cap is missing or not securely attached. • **Do not** re-use a pen.
Storage of PRALUENT • Store unused pen in the refrigerator at 36°F to 46°F (2°C to 8°C) in the outer carton to protect from light. • **Do not** freeze. • **Do not** expose the pen to extreme heat or direct sunlight. • **Do not** shake. • PRALUENT should be allowed to warm to room temperature for 30 to 40 minutes before use. **Do not** keep PRALUENT at room temperature for more than 24 hours. • Keep the PRALUENT pens and all medicines out of the reach of children.	

Keep this leaflet. If you have questions, ask your healthcare provider or call 1-844-PRALUENT (1-844-772-5836).

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



Step A: Getting ready for your injection

Before you start you will need:

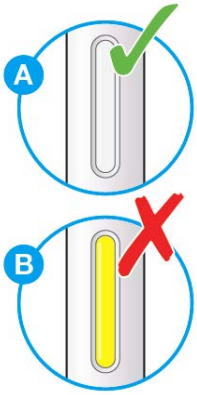
- the PRALUENT pen
- 1 alcohol wipe
- 1 cotton ball or gauze
- a puncture-resistant container (see Step B8)

A1. Look at the label on the pen.

- Check that you have the correct product and the correct dose.
- Check the expiration date: **do not** use if this date has passed.

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.

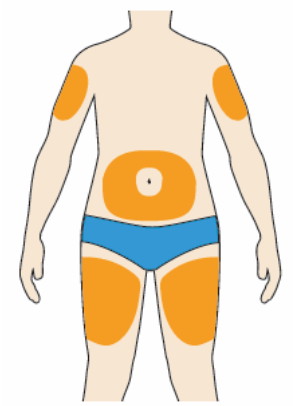
- This is important for administering the entire dose and helps minimize discomfort.
- Take PRALUENT out of the refrigerator to warm up before using.
- **Do not** heat the pen, let it warm up on its own.
- Use the pen as soon as possible after it has warmed up.
- **Do not** put the pen back in the refrigerator.

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:

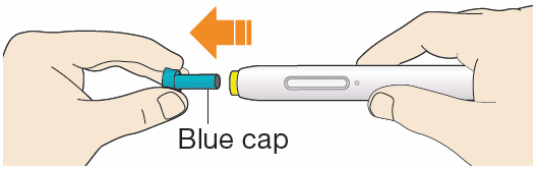
- Change (rotate) your injection site each time you give yourself an injection. If you need to use the same injection area, make sure it is not the same spot on the site you used last time.
- **Do not** inject into areas where the skin is injured, tender, hard, red, or hot. **Do not** inject PRALUENT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



STEP B: How to 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.

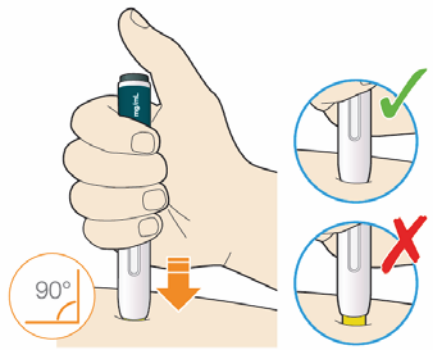


B2: Hold the PRALUENT pen like this.

- **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.

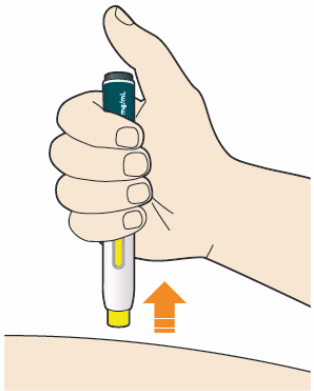
- The injection may take up to 20 seconds.
- The time required for injection to give the entire dose may be longer than for other injectable medicines.

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.

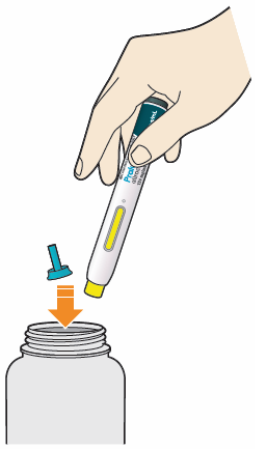
B7: Pull pen away from your skin.

- **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.

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Issue Date: July 2015

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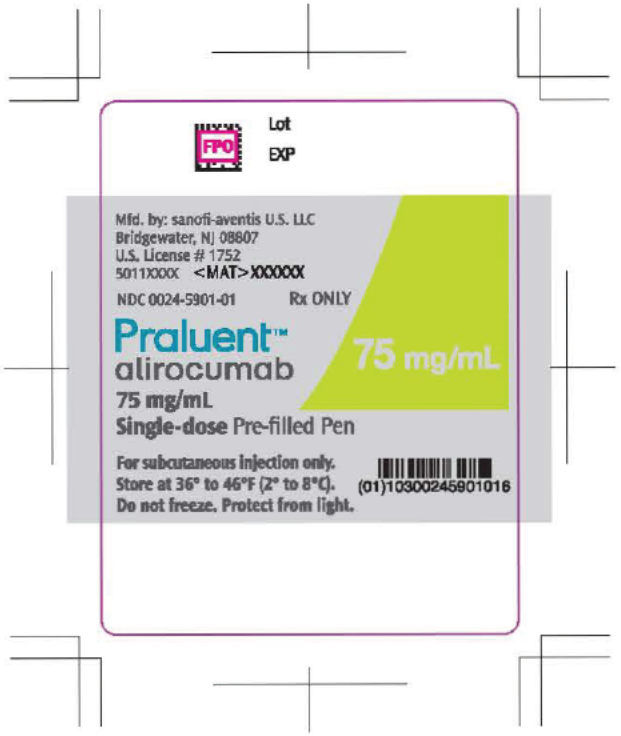

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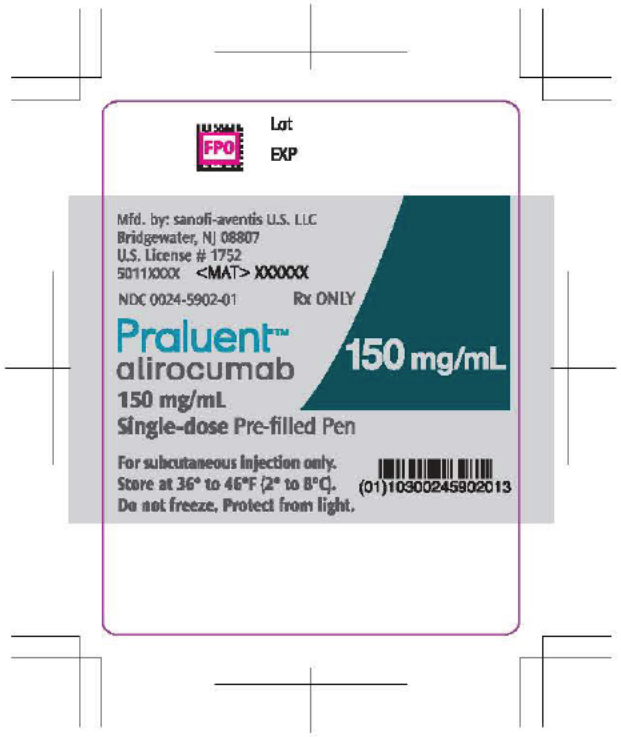

FOR FDA SUBMISSION ONLY

NDC 0024-5903-01

Praluent™
alirocumab
Injection
75 mg/mL
One Pre-filled Syringe

For subcutaneous injection only.

Carton contains: **One** single-dose pre-filled syringe, the Package Insert, Patient Information, and Instructions for Use.

75 mg/mL

FPO

Praluent™
alirocumab
Injection
75 mg/mL
One Pre-filled Syringe
For subcutaneous injection only.
Each single-dose pre-filled syringe contains:
75 mg alirocumab, histidine (8 mM), polysorbate 20 (0.1 mg), sucrose (100 mg), and water for injection, (USP).
Dosage and Administration: See package insert for dosage information and instructions for use.
WARNING: Keep out of reach of children.
Do not use after expiration.
Do not use if seal is broken or package is damaged.
No U.S. standard of potency. Sterile solution - No preservatives.
Store in refrigerator at 36° to 46°F (2° to 8°C).
Do not freeze. Do not expose to extreme heat. Do not shake.
Store in the carton to protect from light.
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and Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591)
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Date of injection:

_____

N 3 00245 90301 3

FPO

XXXXXX

75 mg/mL

FPO

For more information, **scan the QR code** or go to www.praluent.com

NDC 0024-5903-01

Praluent™
alirocumab
Injection
75 mg/mL
One Pre-filled Syringe

For subcutaneous injection only.

Carton contains: **One** single-dose pre-filled syringe, the Package Insert, Patient Information, and Instructions for Use.

NDC 0024-5903-01

Rx ONLY

Praluent™
alirocumab
Injection
75 mg/mL
One Pre-filled Syringe
For subcutaneous injection only. Single-dose.
Carton contains: **One** single-dose pre-filled syringe, the Package Insert, Patient Information, and Instructions for Use.

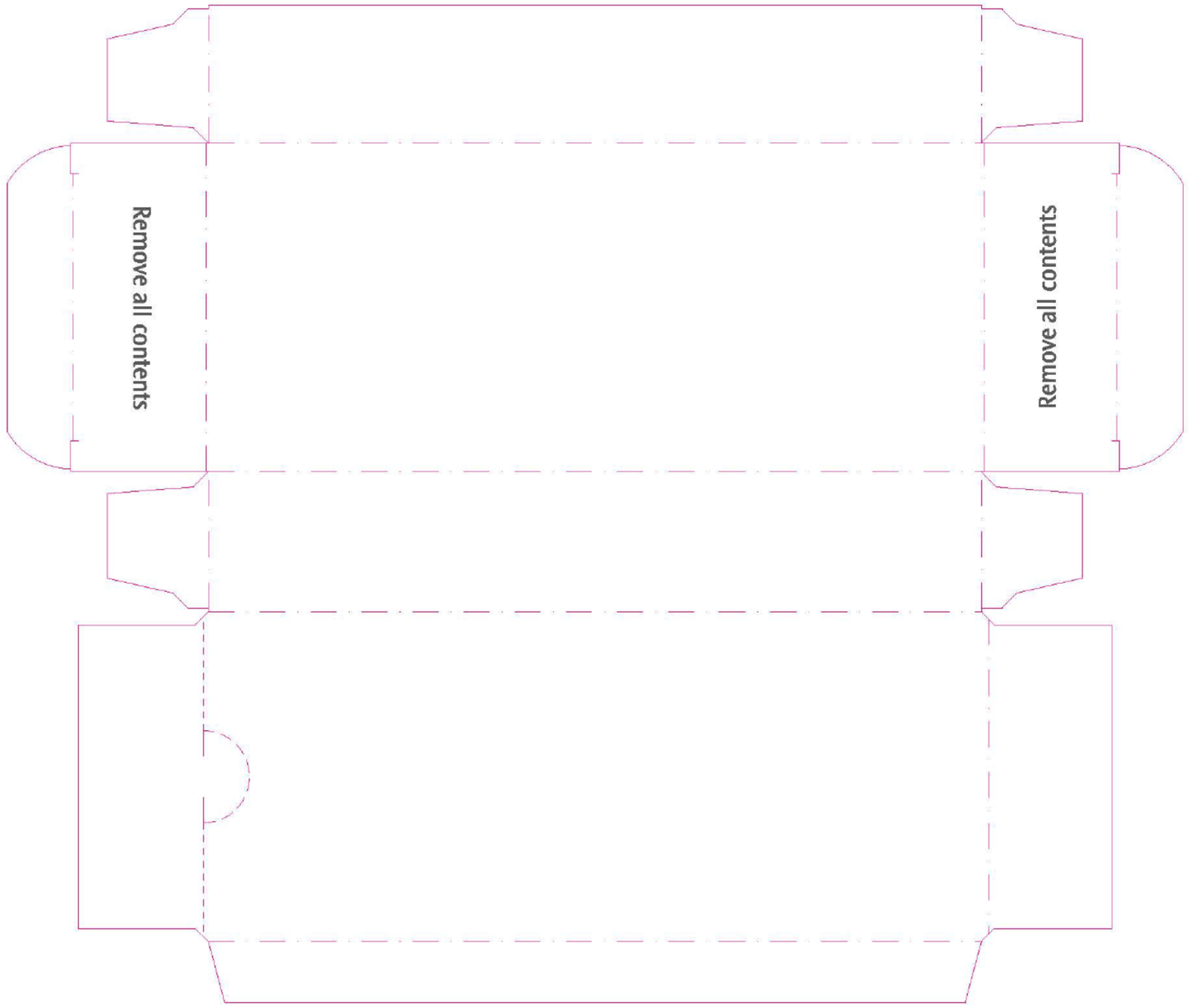
75 mg/mL

OPEN

REGENERON SANOFI

Lot
Exp

FOR FDA SUBMISSION ONLY



FOR FDA SUBMISSION ONLY

NDC 0024-5903-02

Praluent™
alirocumab
Injection
75 mg/mL
Two Pre-filled Syringes

For subcutaneous injection only.
Carton contains: **Two** single-dose pre-filled syringes, the Package Insert, Patient Information, and Instructions for Use.

75 mg/mL

FPO

Praluent™
alirocumab
Injection
75 mg/mL
Two Pre-filled Syringes
For subcutaneous injection only.
Each single-dose pre-filled syringe contains:
75 mg alirocumab, histidine (8 mM), polysorbate 20 (0.1 mg), sucrose (100 mg), and water for injection, (USP).
Dosage and Administration: See package insert for dosage information and instructions for use.
WARNING: Keep out of reach of children.
Do not use after expiration.
Do not use if seal is broken or package is damaged.
No U.S. standard of potency. Sterile solution - No preservatives.
Store in refrigerator at 36° to 46°F (2° to 8°C).
Do not freeze. Do not expose to extreme heat. Do not shake.
Store in the carton to protect from light.
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Date of injection

Syringe 1: _____

Syringe 2: _____

N 3 00245 90302 0

FPO

XXXXXX

75 mg/mL

FPO

For more information, **scan the QR code** or go to www.praluent.com

For subcutaneous injection only.
Carton contains:
Two single-dose pre-filled syringes, the Package Insert, Patient Information, and Instructions for Use.

Praluent™
alirocumab
Injection
75 mg/mL
Two Pre-filled Syringes

NDC 0024-5903-02

NDC 0024-5903-02

Rx ONLY

Praluent™
alirocumab
Injection
75 mg/mL
Two Pre-filled Syringes
For subcutaneous injection only. Single-dose.
Carton contains: **Two** single-dose pre-filled syringes, the Package Insert, Patient Information, and Instructions for Use.

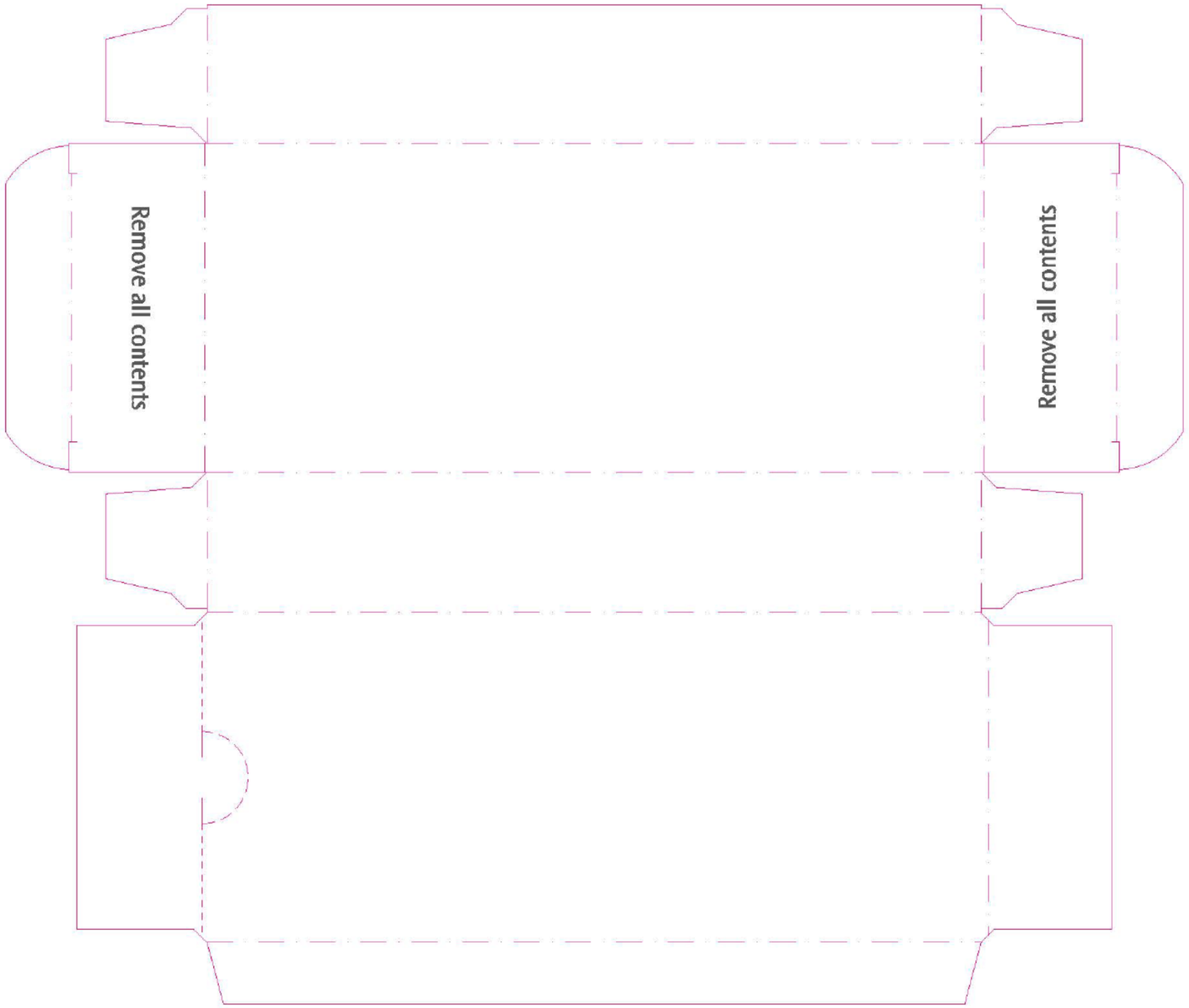
75 mg/mL

OPEN

REGENERON SANOFI

Lot
Exp

FOR FDA SUBMISSION ONLY



FOR FDA SUBMISSION ONLY

NDC 0024-5904-01

Praluent™
alirocumab
Injection
150 mg/mL
One Pre-filled Syringe

For subcutaneous injection only.
Carton contains: One single-dose pre-filled syringe, the Package Insert, Patient Information, and Instructions for Use.

150 mg/mL

FPO

Praluent™
alirocumab
Injection
150 mg/mL
One Pre-filled Syringe
For subcutaneous injection only.
Each single-dose pre-filled syringe contains:
150 mg alirocumab, histidine (6 mM), polysorbate 20 (0.1 mg), sucrose (100 mg), and water for injection, (USP).
Dosage and Administration: See package insert for dosage information and instructions for use.
WARNING: Keep out of reach of children.
Do not use after expiration.
Do not use if seal is broken or package is damaged.
No U.S. standard of potency. Sterile solution - No preservatives.
Store in refrigerator at 36° to 46°F (2° to 8°C).
Do not freeze. Do not expose to extreme heat. Do not shake.
Store in the carton to protect from light.
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Date of injection:

_____

N 3 00245 90401 0

FPO

XXXXXX

150 mg/mL

FPO

For more information, scan the QR code or go to www.praluent.com

NDC 0024-5904-01

Praluent™
alirocumab
Injection
150 mg/mL
One Pre-filled Syringe

For subcutaneous injection only.
Carton contains: One single-dose pre-filled syringe, the Package Insert, Patient Information, and Instructions for Use.

NDC 0024-5904-01

Rx ONLY

Praluent™
alirocumab
Injection
150 mg/mL
One Pre-filled Syringe
For subcutaneous injection only. Single-dose.
Carton contains: **One** single-dose pre-filled syringe, the Package Insert, Patient Information, and Instructions for Use.

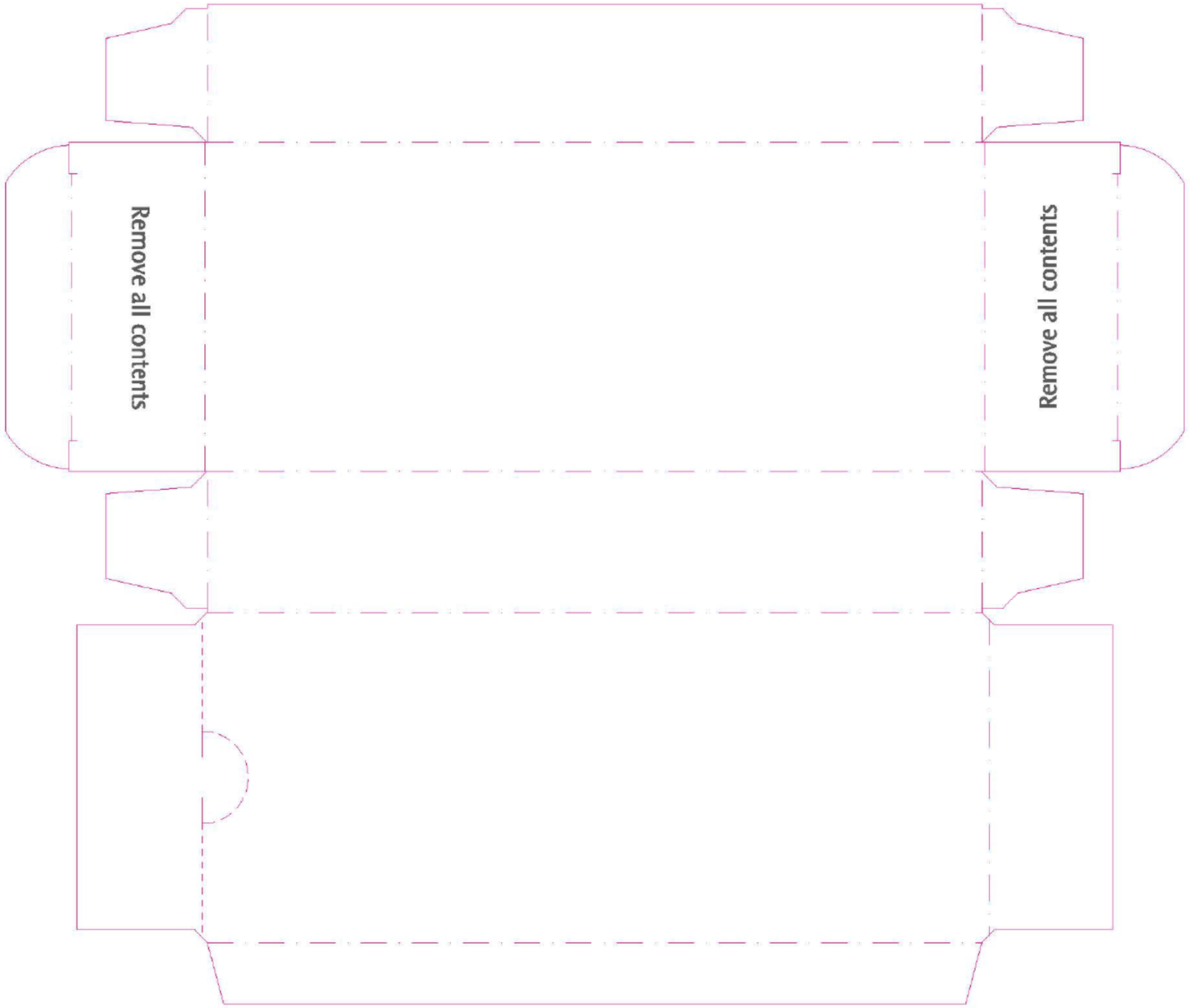
150 mg/mL

OPEN

REGENERON SANOFI

Lot
Exp

FOR FDA SUBMISSION ONLY



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NDC 0024-5904-02

Praluent™
alirocumab
Injection
150 mg/mL
Two Pre-filled Syringes

For subcutaneous injection only.

Carton contains: **Two** single-dose pre-filled syringes, the Package Insert, Patient Information, and Instructions for Use.

150 mg/mL

Praluent™
alirocumab
Injection
150 mg/mL
Two Pre-filled Syringes
For subcutaneous injection only.
Each single-dose pre-filled syringe contains:
150 mg alirocumab, histidine (6 mM), polysorbate 20 (0.1 mg), sucrose (100 mg), and water for injection, (USP).
Dosage and Administration: See package insert for dosage information and instructions for use.
WARNING: Keep out of reach of children.
Do not use after expiration.
Do not use if seal is broken or package is damaged.
No U.S. standard of potency. Sterile solution - No preservatives.
Store in refrigerator at 36° to 46°F (2° to 8°C).
Do not freeze. Do not expose to extreme heat. Do not shake.
Store in the carton to protect from light.
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)
PRALUENT is a trademark of Sanofi
© 2015 Regeneron Pharmaceuticals, Inc. /sanofi-aventis U.S. LLC XXXXXXX

Date of injection

Syringe 1: _____

Syringe 2: _____

FPO

N 3 00245 90402 7

XXXXXX

150 mg/mL

FPO

For more information, **scan the QR code** or go to www.praluent.com

For subcutaneous injection only.
Carton contains:
Two single-dose pre-filled syringes, the Package Insert, Patient Information, and Instructions for Use.

Praluent™
alirocumab
Injection
150 mg/mL
Two Pre-filled Syringes

NDC 0024-5904-02

NDC 0024-**5904**-02

Rx ONLY

Praluent™
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Injection
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150 mg/mL

OPEN

REGENERON SANOFI

Lot
Exp

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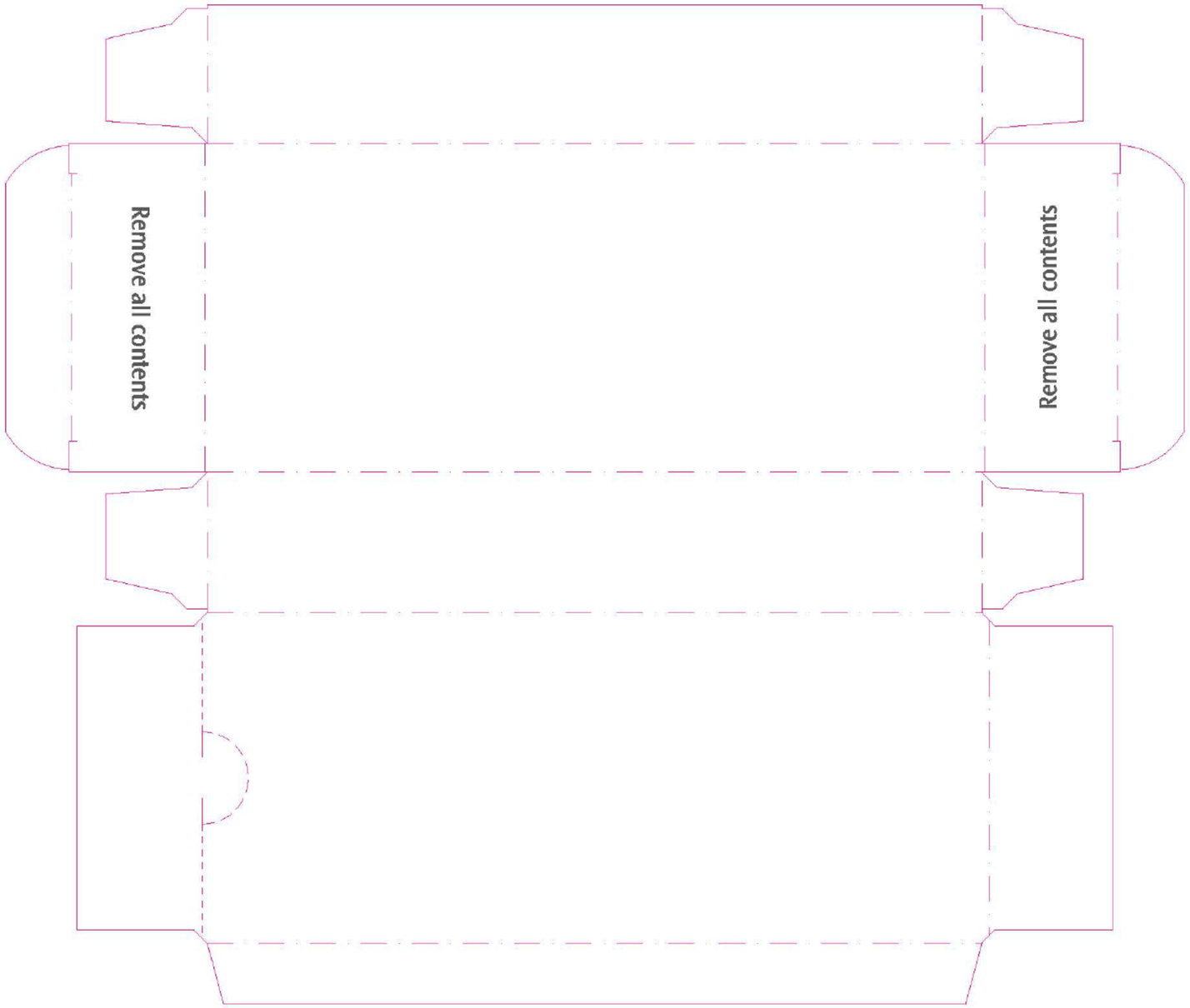

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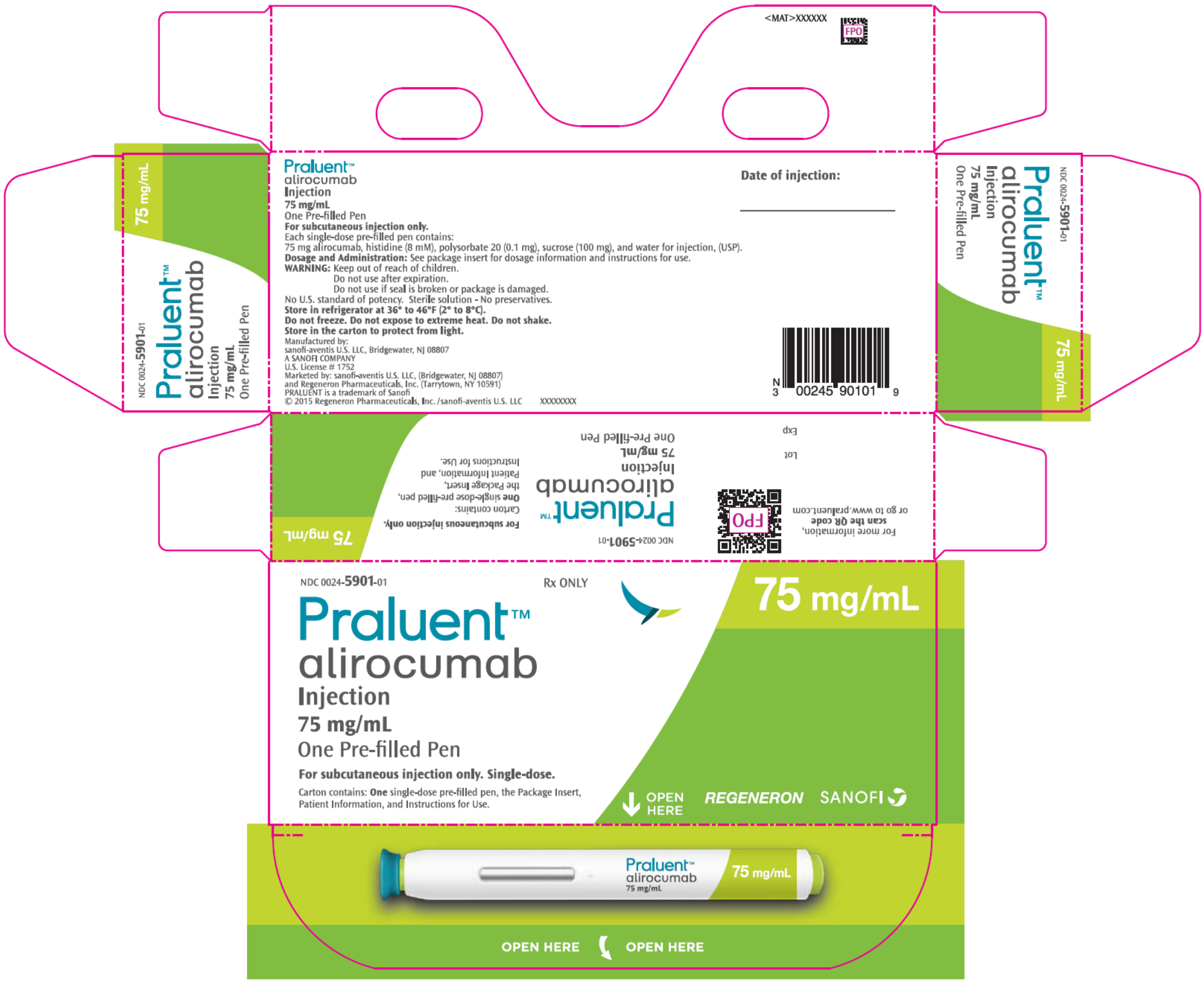

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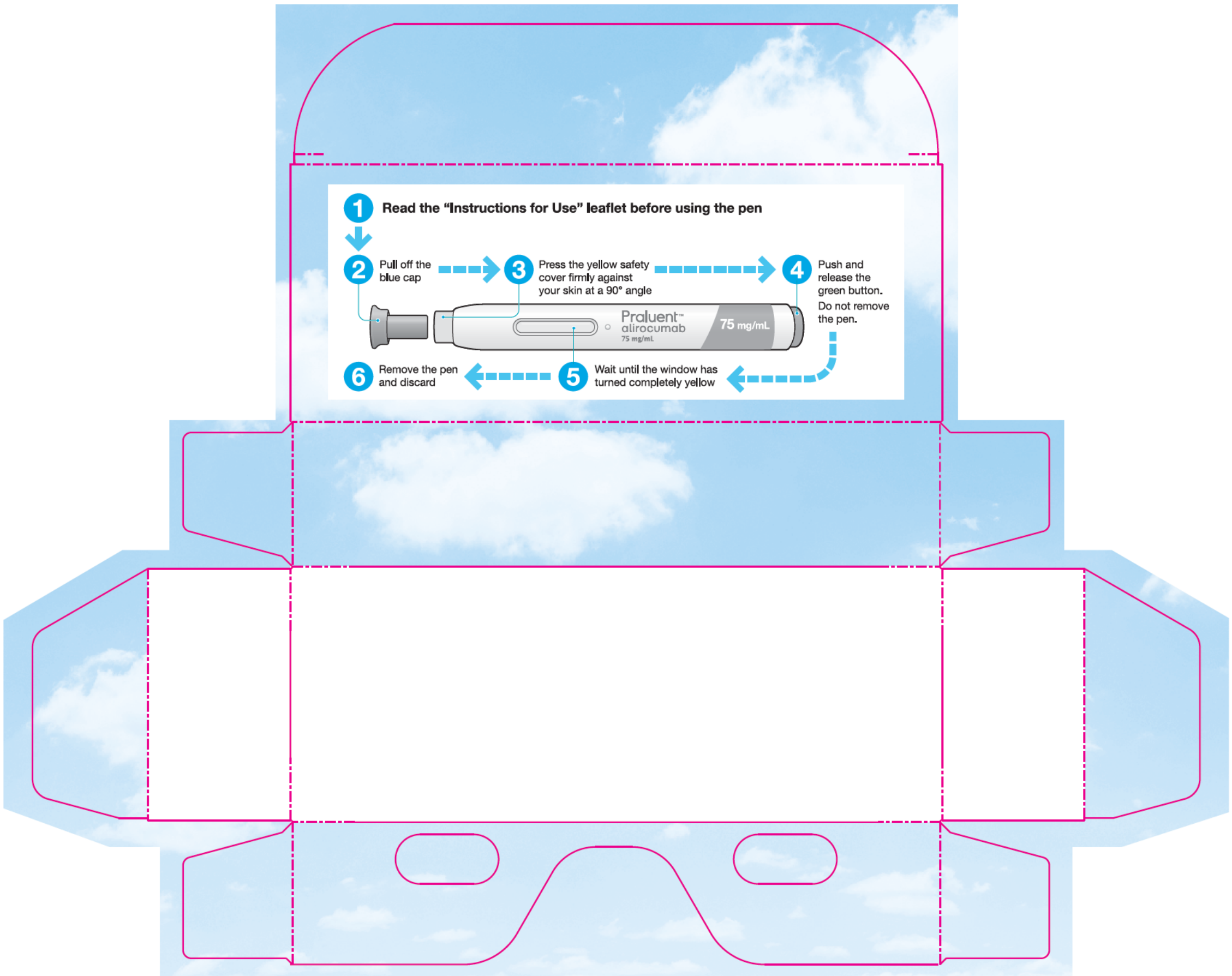

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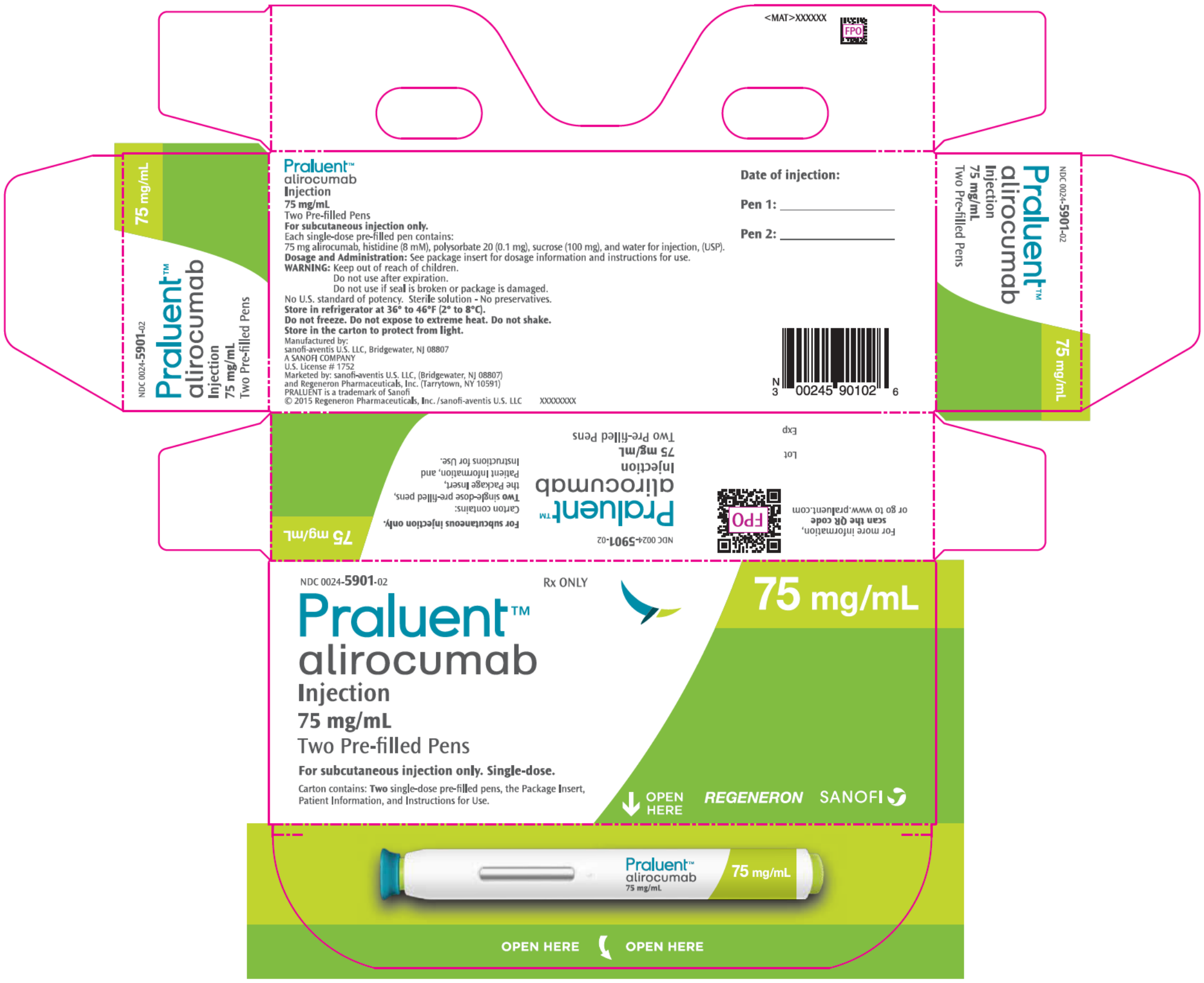

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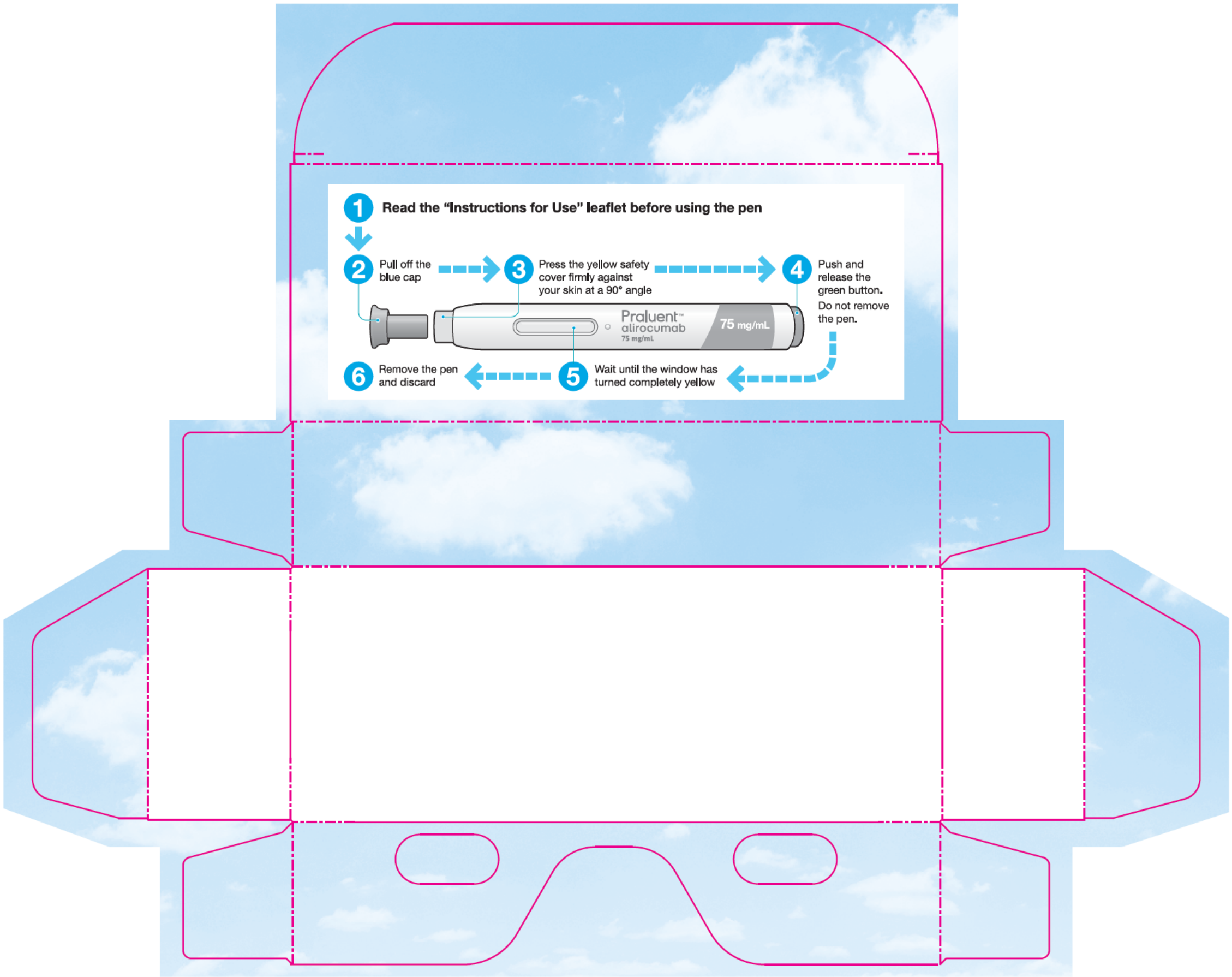

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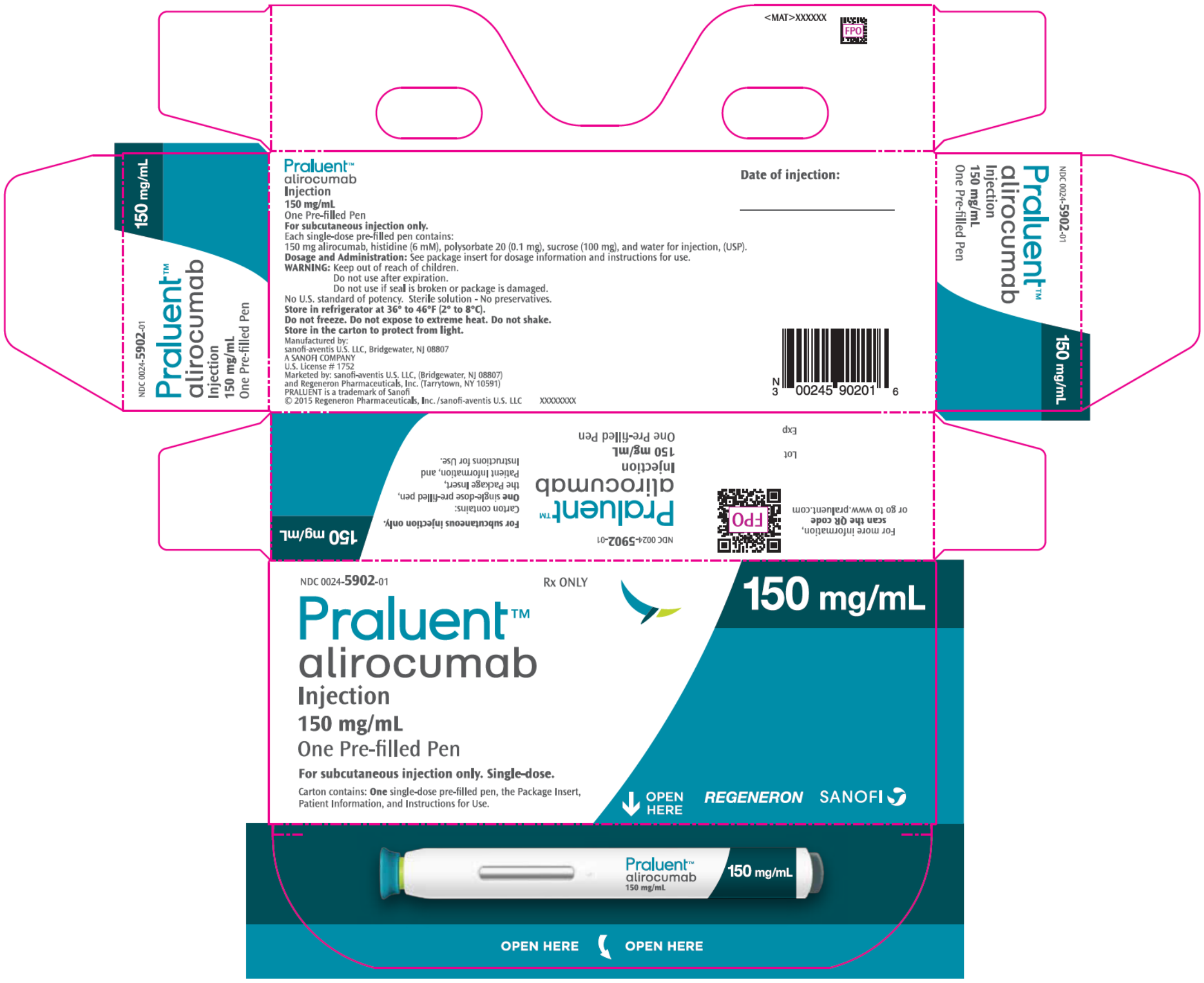

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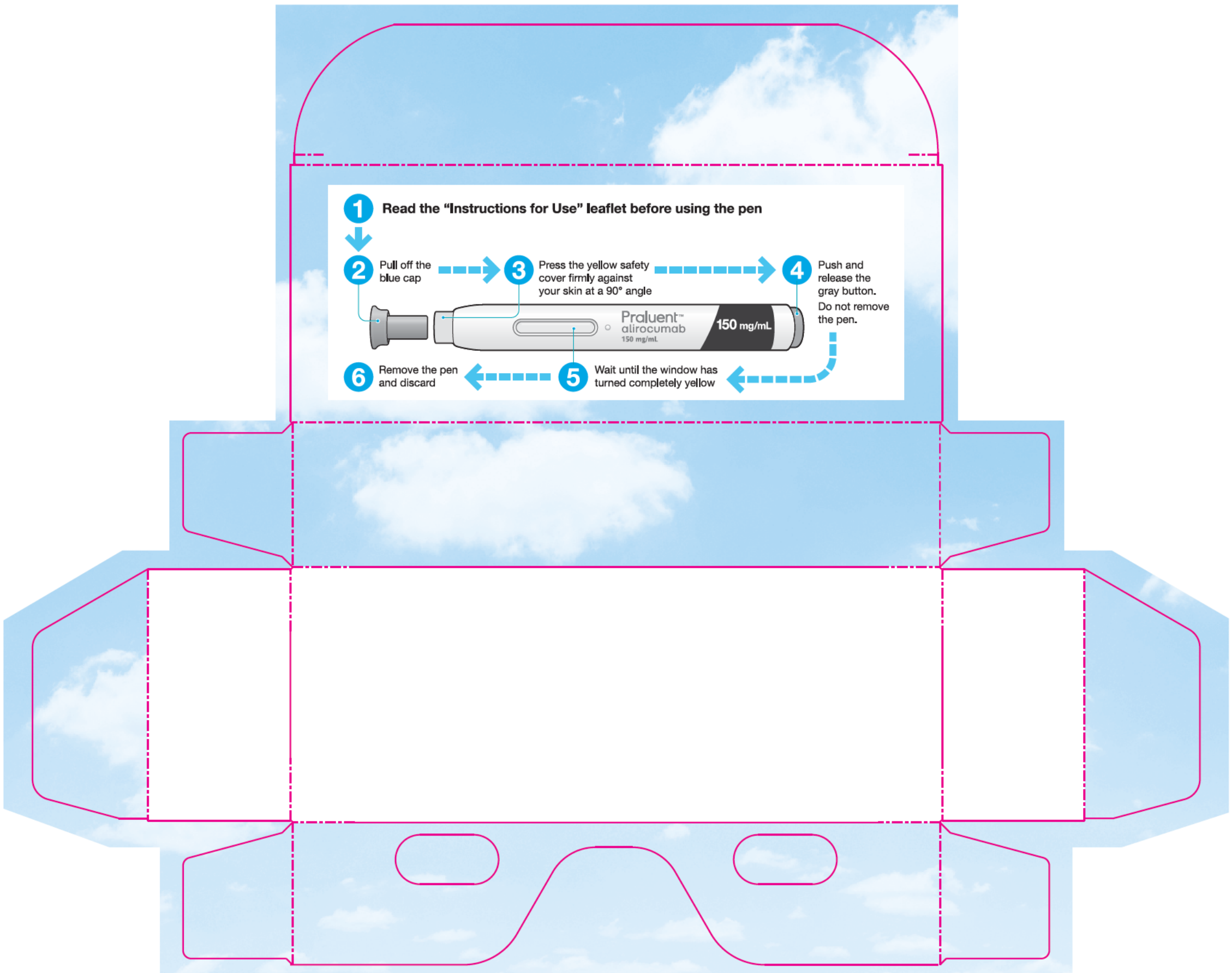

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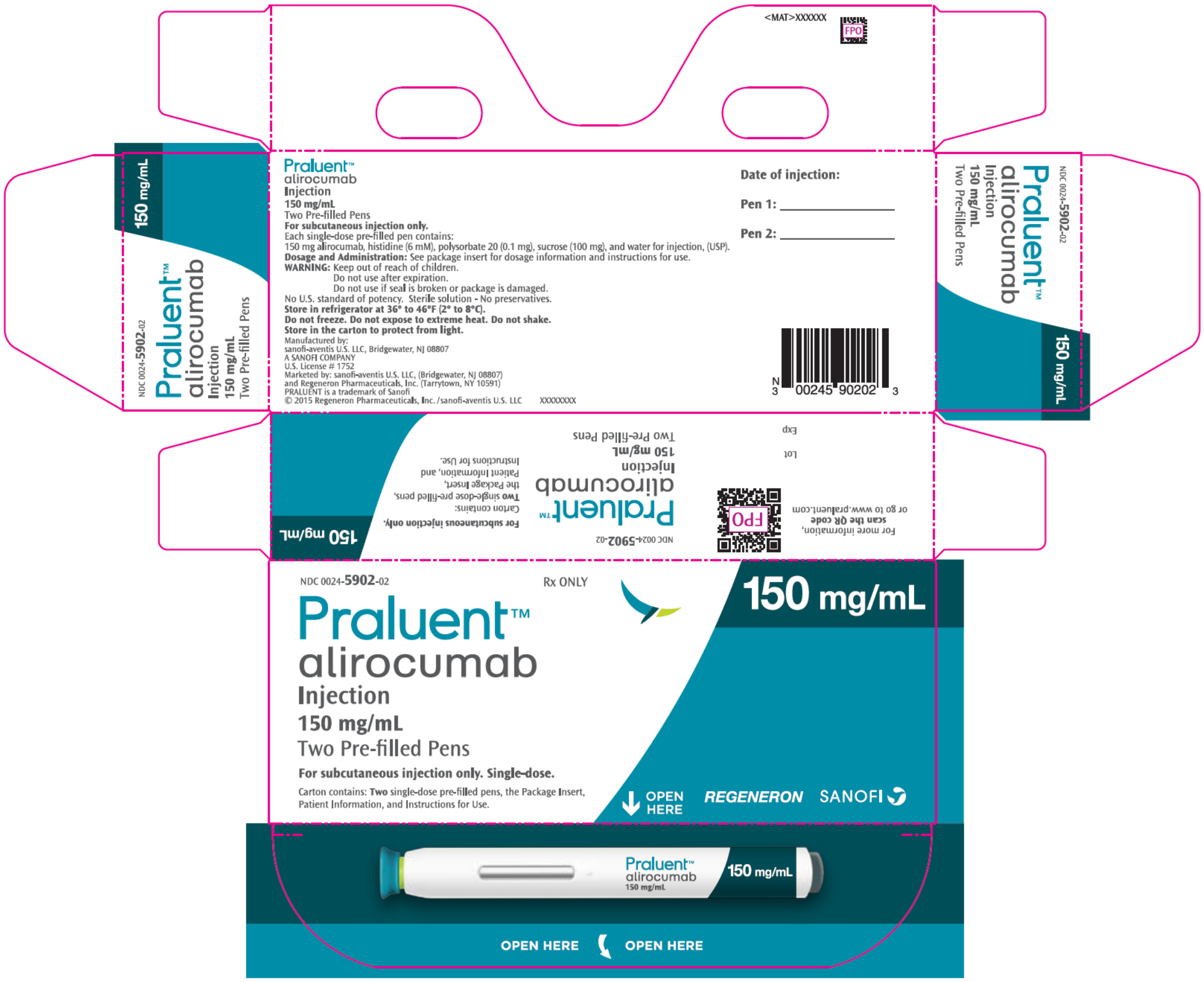

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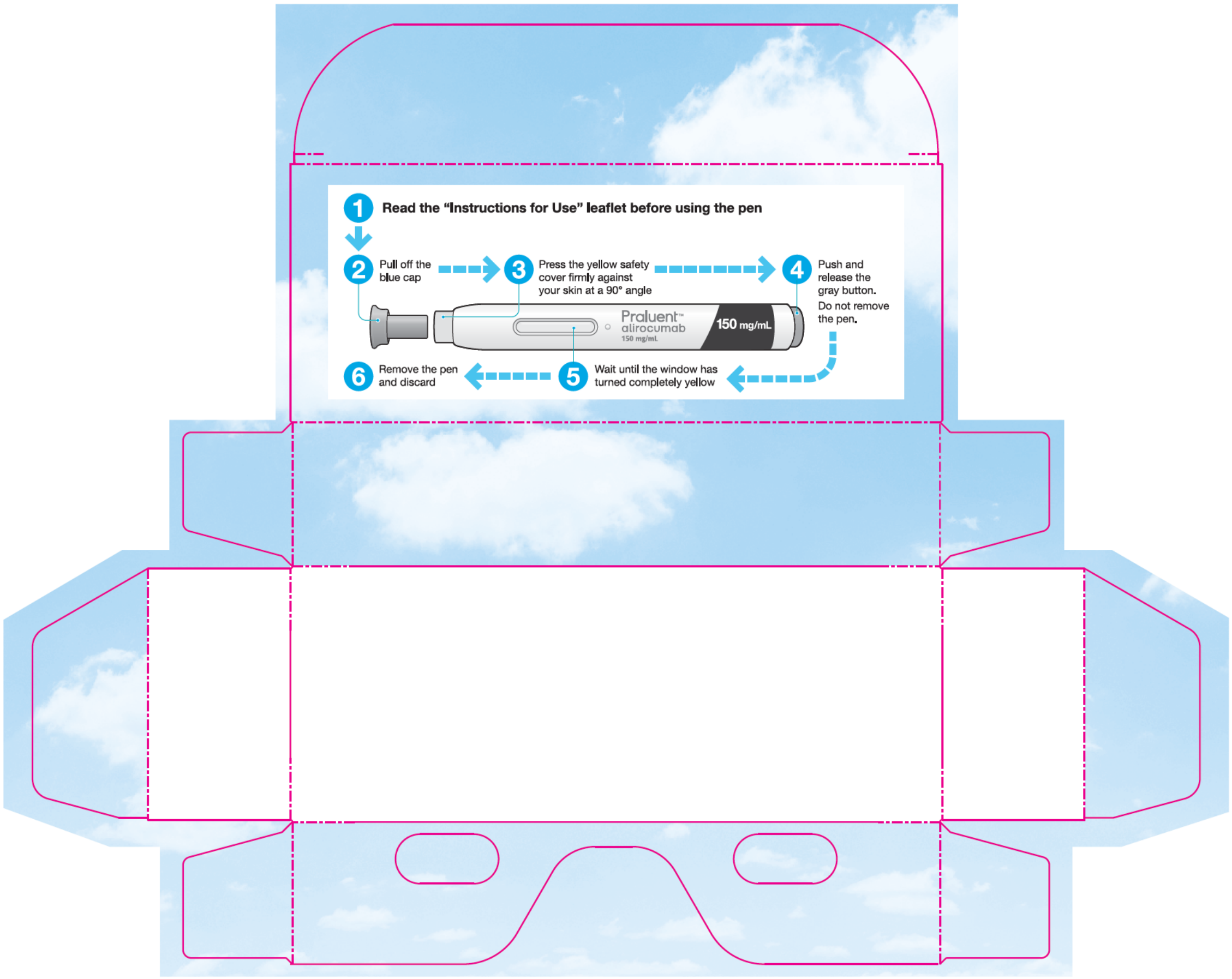

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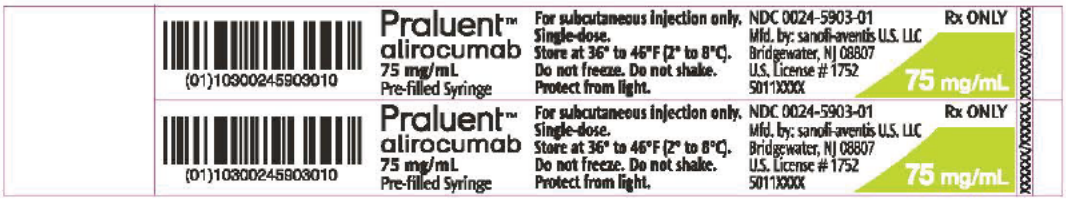
Area for LOT and EXP
variable data printing



FOR FDA SUBMISSION ONLY

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variable data printing

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/s/

MARY H PARKS
07/24/2015

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