ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Praluent 75 mg solution for injection in pre-filled pen
Praluent 150 mg solution for injection in pre-filled pen
Praluent 75 mg solution for injection in pre-filled syringe
Praluent 150 mg solution for injection in pre-filled syringe
Praluent 300 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Praluent 75 mg solution for injection in pre-filled pen

Each single-use pre-filled pen contains 75 mg alirocumab in 1 ml solution.

Praluent 75 mg solution for injection in pre-filled syringe

Each single-use pre-filled syringe contains 75 mg alirocumab in 1 ml solution.

Praluent 150 mg solution for injection in pre-filled pen

Each single-use pre-filled pen contains 150 mg alirocumab in 1 ml solution.

Praluent 150 mg solution for injection in pre-filled syringe

Each single-use pre-filled syringe contains 150 mg alirocumab in 1 ml solution.

Praluent 300 mg solution for injection in pre-filled pen

Each single-use pre-filled pen contains 300 mg alirocumab in 2 ml solution.

Alirocumab is a human IgG1 monoclonal antibody produced in Chinese Hamster Ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear, colourless to pale yellow solution.

pH: 5.7 – 6.3

Osmolality:

Praluent 75 mg solution for injection
293 - 439 mOsm/kg

Praluent 150 mg solution for injection
383 - 434 mOsm/kg

Praluent 300 mg solution for injection
383 – 434 mOsm/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary hypercholesterolaemia and mixed dyslipidaemia

Praluent is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Established atherosclerotic cardiovascular disease

Praluent is indicated in adults with established atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

For study results with respect to effects on LDL-C, cardiovascular events and populations studied see section 5.1.

4.2 Posology and method of administration

Posology

Prior to initiating alirocumab secondary causes of hyperlipidaemia or mixed dyslipidaemia (e.g., nephrotic syndrome, hypothyroidism) should be excluded.

The usual starting dose for alirocumab is 75 mg administered subcutaneously once every 2 weeks. Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg once every 2 weeks, or 300 mg once every 4 weeks (monthly), administered subcutaneously.

The dose of alirocumab can be individualised based on patient characteristics such as baseline LDL-C level, goal of therapy, and response. Lipid levels can be assessed 4 to 8 weeks after treatment initiation or titration, and dose adjusted accordingly (up-titration or down-titration). If additional LDL-C reduction is needed in patients treated with 75 mg once every 2 weeks or 300 mg once every 4 weeks (monthly), the dosage may be adjusted to the maximum dosage of 150 mg once every 2 weeks.

If a dose is missed, the patient should administer the injection as soon as possible and thereafter resume treatment on the original schedule.

Special populations

Elderly

No dose adjustment is needed for elderly patients.

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 section 5.2).

Renal impairment

No dose adjustment is needed for patients with mild or moderate renal impairment. Limited data are available in patients with severe renal impairment (see section 5.2).

Body weight

No dose adjustment is needed in patients based on weight.

Paediatric population

The safety and efficacy of Praluent in children and adolescents less than 18 years of age have not been established. Currently available data are described in sections 4.8, 5.1, and 5.2 but no recommendation on a posology can be made. Alirocumab has not been studied in paediatric patients less than 8 years of age.

Method of administration

Subcutaneous use.

Alirocumab is injected as a subcutaneous injection into the thigh, abdomen or upper arm.

Each pre-filled pen or pre-filled syringe is for single use only.

To administer the 300 mg dose, either one 300 mg injection or two 150 mg injections should be given consecutively at two different injection sites.

It is recommended to rotate the injection site with each injection.

Alirocumab should not be injected into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections.

Alirocumab must not be co-administered with other injectable medicinal products at the same injection site.

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

Precautions to be taken before handling or administering the medicinal product
The solution should be allowed to warm to room temperature prior to use (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Allergic reactions

General allergic reactions, including pruritus, as well as rare and sometimes serious allergic reactions such as hypersensitivity, nummular eczema, urticaria, and hypersensitivity vasculitis have been reported in clinical studies. Angioedema has been reported in the postmarketing setting (see section 4.8). If signs or symptoms

of serious allergic reactions occur, treatment with alirocumab must be discontinued and appropriate symptomatic treatment initiated (see section 4.3).

Renal impairment

In clinical studies, there was limited representation of patients with severe renal impairment (defined as eGFR < 30 ml/min/1.73 m^2) (see section 5.2). Alirocumab should be used with caution in patients with severe renal impairment.

Hepatic impairment

Patients with severe hepatic impairment (Child-Pugh C) have not been studied (see section 5.2). Alirocumab should be used with caution in patients with severe hepatic impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of alirocumab on other medicinal products

Since alirocumab is a biological medicinal product, no pharmacokinetic effects of alirocumab on other medicinal products and no effect on cytochrome P450 enzymes are anticipated.

Effects of other medicinal products on alirocumab

Statins and other lipid-modifying therapy are known to increase production of PCSK9, the protein targeted by alirocumab. This leads to the increased target-mediated clearance and reduced systemic exposure of alirocumab. Compared to alirocumab monotherapy, the exposure to alirocumab is about 40%, 15%, and 35% lower when used concomitantly with statins, ezetimibe, and fenofibrate, respectively. However, reduction of LDL-C is maintained during the dosing interval when alirocumab is administered every two weeks.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Praluent in pregnant women. Alirocumab is a recombinant IgG1 antibody, therefore it is expected to cross the placental barrier (see section 5.3).
Animal studies do not indicate direct or indirect harmful effects with respect to maintenance of pregnancy or embryo-foetal development; maternal toxicity was noted in rats, but not in monkeys at doses in excess of the human dose, and a weaker secondary immune response to antigen challenge was observed in the offspring of monkeys (see section 5.3).
The use of Praluent is not recommended during pregnancy unless the clinical condition of the woman requires treatment with alirocumab.

Breast-feeding

It is not known whether alirocumab is excreted in human milk. Human immunoglobulin G (IgG) is excreted in human milk, in particular in colostrum; the use of Praluent is not recommended in breast-feeding women during this period. For the remaining duration of breast-feeding, exposure is expected to be low.
Since the effects of alirocumab on the breast-fed infant are unknown, a decision should be made whether to discontinue nursing or to discontinue Praluent during this period.

Fertility

In animal studies, there were no adverse effects on surrogate markers of fertility (see section 5.3). There are no data on adverse effects on fertility in humans.

4.7 Effects on ability to drive and use machines

Praluent has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions, at recommended doses, are local injection site reactions (6.1%), upper respiratory tract signs and symptoms (2.0%), and pruritus (1.1%). Most common adverse reactions leading to treatment discontinuation in patients treated with alirocumab were local injection site reactions.
The safety profile in ODYSSEY OUTCOMES was consistent with the overall safety profile described in the phase 3 controlled trials.

No difference in the safety profile was observed between the two doses (75 mg and 150 mg) used in the phase 3 program.

Tabulated list of adverse reactions

The following adverse reactions were reported in patients treated with alirocumab in pooled controlled studies and/or post-marketing use (see Table 1).

Frequencies for all adverse reactions identified from clinical trials have been calculated based on their incidence in pooled phase 3 clinical trials. Adverse reactions are presented by system organ class. Frequency categories are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data).

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse reactions is qualified as "not known".

Table 1 – Adverse reactions

System organ class	Common	Rare	Not known
Immune system disorders		Hypersensitivity, hypersensitivity vasculitis	
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract signs and symptoms*		
Skin and subcutaneous tissue disorders	Pruritus	Urticaria, eczema nummular	Angioedema
General disorders and administration site conditions	Injection site reactions**		Flu-like illness

* including mainly oropharyngeal pain, rhinorrhea, sneezing

** including erythema/redness, itching, swelling, pain/tenderness

Description of selected adverse reactions

Local injection site reactions

Local injection site reactions, including erythema/redness, itching, swelling, and pain/tenderness, were reported in 6.1% of patients treated with alirocumab versus 4.1% in the control group (receiving placebo injections). Most injection site reactions were transient and of mild intensity. The discontinuation rate due to local injection site reactions was comparable between the two groups (0.2% in the alirocumab group versus 0.3% in the control group). In the cardiovascular outcomes study (ODYSSEY OUTCOMES), injection site reactions also occurred more frequently in alirocumab-treated patients than in placebo-treated patients (3.8% alirocumab versus 2.1% placebo).

General allergic reactions

General allergic reactions were reported more frequently in the alirocumab group (8.1% of patients) than in the control group (7.0% of patients), mainly due to a difference in the incidence of pruritus. The observed cases of pruritus were typically mild and transient. In addition, rare and sometimes serious allergic reactions such as hypersensitivity, nummular eczema, urticaria, and hypersensitivity vasculitis have been reported in controlled clinical studies (see section 4.4). In the cardiovascular outcomes study (ODYSSEY OUTCOMES), general allergic reactions were similar in alirocumab-treated patients and placebo-treated patients (7.9% alirocumab, 7.8% placebo). No difference was seen in the incidence of pruritus.

Special populations

Elderly

Although no safety issues were observed in patients over 75 years of age, data are limited in this age group. In the phase 3 primary hypercholesterolemia and mixed dyslipidaemia controlled studies, 1,158 patients (34.7%) treated with alirocumab were ≥65 years of age and 241 patients (7.2%) treated with alirocumab were ≥75 years of age. In the cardiovascular outcomes controlled study, 2,505 patients (26.5%) treated with alirocumab were ≥65 years of age and 493 patients (5.2%) treated with alirocumab were ≥75 years of age. There were no significant differences observed in safety and efficacy with increasing age.

Paediatric population

The experience of alirocumab in paediatric patients is limited to 18 patients aged 8 to 17 years with homozygous familial hypercholesterolaemia (HoFH). No new safety finding was observed compared to the known adult safety profile.

Every 4 week dosing study

The safety profile in patients treated with a 300 mg once every 4 week (monthly) dosing regimen was similar to the safety profile as described for the clinical studies program using a 2 week dosing regimen, except for a higher rate of local injection site reactions. Local injection site reactions were reported overall at a frequency of 16.6% in the 300 mg once every 4 weeks treatment group and 7.9% in the placebo group. Patients in the alirocumab 300 mg every 4 weeks treatment group received alternating placebo injections to maintain blinding in regard to injection frequency. Excluding injection site reactions (ISRs) that occurred after these placebo injections, the frequency of ISRs was 11.8%. The discontinuation rate due to injection site reactions was 0.7% in the 300 mg once every 4 weeks treatment group and 0% in the placebo group.

LDL-C values <25 mg/dL (<0.65 mmol/L)

In all clinical studies background lipid lowering therapies could not be adjusted by trial design. The percentage of patients who reached LDL-C values <25 mg/dL (<0.65 mmol/L) depended both on the baseline LDL-C and the dose of alirocumab.

In a pool of controlled studies using a 75 mg every 2 week (Q2W) starting dose and in which the dose was increased to 150 mg Q2W if the patient's LDL-C was not <70 mg/dL or < 100 mg/dL (1.81 mmol/L or 2.59 mmol/L), 29.3% of patients with baseline LDL-C <100 mg/dL and 5.0% of patients with baseline LDL-C ≥100 mg/dL treated with alirocumab had two consecutive values of LDL-C <25 mg/dL (<0.65 mmol/L). In the ODYSSEY OUTCOMES study, in which the starting alirocumab dose was 75 mg Q2W and the dose was increased to 150 mg Q2W if the patient's LDL-C was not <50 mg/dL (1.29 mmol/L), 54.8% of patients with baseline LDL-C <100 mg/dL and 24.2% of patients with baseline LDL-C ≥100 mg/dL treated with alirocumab had two consecutive values of LDL-C <25 mg/dL (<0.65 mmol/L).

Although adverse consequences of very low LDL-C were not identified in alirocumab trials, the long-term effects of sustained very low levels of LDL-C are unknown.

Immunogenicity/ Anti-drug-antibodies (ADA)

In the ODYSSEY OUTCOMES trial, 5.5% of patients treated with alirocumab 75 mg and/or 150 mg every 2 weeks (Q2W) had anti-drug antibodies (ADA) detected after initiating treatment compared with 1.6% of patients treated with placebo, most of these were transient responses. Persistent ADA responses were observed in 0.7% of patients treated with alirocumab and 0.4% of patients treated with placebo. Neutralising antibody (NAb) responses were observed in 0.5% of patients treated with alirocumab and in <0.1% of patients treated with placebo.

Anti-drug antibody responses, including NAb, were low titer and did not appear to have a clinically meaningful impact on the efficacy or safety of alirocumab, except for a higher rate of injection site reactions in patients with treatment emergent ADA compared to patients who were ADA negative (7.5% vs 3.6%). The long-term consequences of continuing alirocumab treatment in the presence of ADA are unknown. In a pool of ten placebo-controlled and active-controlled trials of patients treated with alirocumab 75 mg and/or 150 mg Q2W as well as in a separate clinical study of patients treated with alirocumab 75 mg Q2W or 300 mg every 4 weeks (including some patients with dose adjustment to 150 mg Q2W), the incidence of detecting ADA and NAb was similar to the results from the ODYSSEY OUTCOMES trial described above.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific treatment for alirocumab overdose. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: lipid modifying agents, other lipid modifying agents, ATC code: C10AX14.

Mechanism of action

Alirocumab is a fully human IgG1 monoclonal antibody that binds with high affinity and specificity to proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 binds to the low-density lipoprotein receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. LDLR is the primary receptor that clears circulating LDL, therefore the decrease in LDLR levels by PCSK9 results in higher blood levels of LDL-C. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs available to clear LDL, thereby lowering LDL-C levels.

The LDLR also binds triglyceride-rich VLDL remnant lipoproteins and intermediate-density lipoprotein (IDL). Therefore, alirocumab treatment can produce reductions in these remnant lipoproteins as evidenced by its reductions in apolipoprotein B (Apo B), non-high-density lipoprotein cholesterol (non-HDL-C) and triglycerides (TG). Alirocumab also results in reductions in lipoprotein (a) [Lp(a)], which is a form of LDL that is bound to apolipoprotein (a). However, the LDLR has been shown to have a low affinity for Lp(a), therefore the exact mechanism by which alirocumab lowers Lp(a) is not fully understood.

In genetic studies in humans, PCSK9 variants with either loss-of-function or gain-of-function mutations have been identified. Individuals with single allele PCSK9 loss-of-function mutation have lower levels of LDL-C, which correlated with a significantly lower incidence of coronary heart disease. A few individuals have been reported, who carry PCSK9 loss-of-function mutations in two alleles and have profoundly low LDL-C levels, with HDL-C and TG levels in the normal range. Conversely, gain-of-function mutations in the PCSK9 gene have been identified in patients with increased LDL-C levels and a clinical diagnosis of familial hypercholesterolaemia.

In a multicenter, double-blind, placebo-controlled, 14 week study, 13 patients with heterozygous familial hypercholesterolaemia (heFH) due to gain-of-function mutations in the PCSK9 gene were randomised to receive either alirocumab 150 mg Q2W or placebo. Mean baseline LDL-C was 151.5 mg/dL (3.90 mmol/L). At week 2, the mean reduction from baseline in LDL-C was 62.5% in the alirocumab-treated patients as compared to 8.8% in the placebo patients. At week 8, the mean reduction in LDL-C from baseline with all patients treated with alirocumab was 72.4%.

Pharmacodynamic effects

In *in vitro* assays, alirocumab did not induce Fc-mediated effector function activity (antibody-dependent cell-mediated toxicity and complement-dependent cytotoxicity) either in the presence or absence of PCSK9 and no soluble immune complexes capable of binding complement proteins were observed for alirocumab when bound to PCSK9.

Clinical efficacy and safety in primary hypercholesterolaemia and mixed dyslipidaemia

Summary of the Phase 3 Clinical Trials Program - 75 mg and/or 150 mg every 2 weeks (Q2W) dosing regimen

The efficacy of alirocumab was investigated in ten phase 3 trials (five placebo-controlled and five ezetimibe-controlled studies), involving 5,296 randomised patients with hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, with 3,188 patients randomised to alirocumab. In the phase 3 studies, 31% of patients had type 2 diabetes mellitus, and 64% of patients had a history of coronary heart disease. Three of the ten studies were conducted exclusively in patients with heterozygous familial hypercholesterolaemia (heFH). The majority of patients in the phase 3 program were taking background lipid-modifying therapy consisting of a maximally tolerated dose of statin, with or without other lipid-modifying therapies, and were at high or very high cardiovascular (CV) risk. Two studies were conducted in patients who were not concomitantly treated with a statin, including one study in patients with documented statin intolerance.

Two studies (*LONG TERM* and *HIGH FH*), involving a total of 2,416 patients, were performed with a 150 mg every 2 weeks (Q2W) dose only. Eight studies were performed with a dose of 75 mg Q2W, and criteria-based up-titration to 150 mg Q2W at week 12 in patients who did not achieve their pre-defined target LDL-C based on their level of CV risk at week 8.

The primary efficacy endpoint in all of the phase 3 studies was the mean percent reduction from baseline in LDL-C at week 24 as compared to placebo or ezetimibe. All of the studies met their primary endpoint. In general, administration of alirocumab also resulted in a statistically significant greater percent reduction in total cholesterol (Total-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (Apo B), and lipoprotein (a) [Lp(a)] as compared to placebo/ ezetimibe, whether or not patients were

concomitantly being treated with a statin. Alirocumab also reduced triglycerides (TG), and increased high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-1 (Apo A-1) as compared to placebo. For detailed results see Table 2 below. Reduction in LDL-C was seen across age, gender, body mass index (BMI), race, baseline LDL-C levels, patients with heFH and non-heFH, patients with mixed dyslipidaemia, and diabetic patients. Although similar efficacy was observed in patients over 75 years, data are limited in this age group. LDL-C reduction was consistent regardless of concomitantly used statins and doses. A significantly higher proportion of patients achieved an LDL-C of <70 mg/dL (<1.81 mmol/L) in the alirocumab group as compared to placebo or ezetimibe at week 12 and week 24. In studies using the criteria-based up-titration regimen, a majority of patients achieved the pre-defined target LDL-C (based on their level of CV risk) on the 75 mg Q2W dose, and a majority of patients maintained treatment on the 75 mg Q2W dose. The lipid-lowering effect of alirocumab was observed within 15 days after the first dose reaching maximum effect at approximately 4 weeks. With long-term treatment, efficacy was sustained over the duration of the studies (up to 2 years). Following discontinuation of alirocumab, no rebound in LDL-C was observed, and LDL-C levels gradually returned to baseline levels.

In pre-specified analyses before possible up-titration at week 12 in the 8 studies in which patients started with the 75 mg every 2 weeks dosing regimen, mean reductions in LDL-C ranging from 44.5% to 49.2% were achieved. In the 2 studies in which patients were started and maintained on 150 mg every 2 weeks, the achieved mean reduction of LDL-C at week 12 was 62.6%. In analyses of pooled phase 3 studies that allowed up-titration, among the subgroup of patients up-titrated, an increase from 75 mg Q2W to 150 mg Q2W alirocumab at week 12 resulted in an additional 14% mean reduction in LDL-C in patients on a background statin. In patients not on a background statin, up-titration of alirocumab resulted in an additional 3% mean reduction in LDL-C, with the majority of the effect seen in approximately 25% of patients who achieved at least an additional 10% LDL-C lowering after up-titration. Patients up-titrated to 150 mg Q2W had a higher mean baseline LDL-C.

Evaluation of cardiovascular (CV) events

In pre-specified analyses of pooled phase 3 studies, treatment-emergent CV events confirmed by adjudication, consisting of coronary heart disease (CHD) death, myocardial infarction, ischemic stroke, unstable angina requiring hospitalisation, congestive heart failure hospitalisation, and revascularisation, were reported in 110 (3.5%) patients in the alirocumab group and 53 (3.0%) patients in the control group (placebo or active control) with HR=1.08 (95% CI, 0.78 to 1.50). Major adverse cardiovascular events ("MACE-plus", i.e.: CHD death, myocardial infarction, ischemic stroke, and unstable angina requiring hospitalisation) confirmed by adjudication were reported in 52 of 3,182 (1.6%) patients in the alirocumab group and 33 of 1,792 (1.8%) patients in the control group (placebo or active control); HR=0.81 (95% CI, 0.52 to 1.25).

In pre-specified final analyses of the LONG TERM study, treatment-emergent CV events confirmed by adjudication occurred in 72 of 1,550 (4.6%) patients in the alirocumab group and in 40 of 788 (5.1%) patients in the placebo group; MACE-plus confirmed by adjudication were reported in 27 of 1,550 (1.7%) patients in the alirocumab group and 26 of 788 (3.3%) patients in the placebo group. Hazard ratios were calculated post-hoc; for all CV events, HR=0.91 (95% CI, 0.62 to 1.34); for MACE-plus, HR=0.52 (95% CI, 0.31 to 0.90).

All-cause mortality

All-cause mortality in phase 3 studies was 0.6% (20 of 3,182 patients) in the alirocumab group and 0.9% (17 of 1,792 patients) in the control group. The primary cause of death in the majority of these patients was CV events.

Combination therapy with a statin

Placebo-controlled phase 3 studies (on background statin) in patients with primary hypercholesterolaemia or mixed dyslipidaemia

LONG TERM study

This multicenter, double-blind, placebo-controlled, 18-month study included 2,310 patients with primary hypercholesterolaemia at high or very high CV risk and on a maximally tolerated dose of statin, with or without other lipid-modifying therapy. Patients received either alirocumab at a dose of 150 mg Q2W or placebo in addition to their existing lipid-modifying therapy. The LONG TERM study included 17.7% heFH patients, 34.6% with type 2 diabetes mellitus, and 68.6% with a history of coronary heart disease. At week 24, the mean treatment difference from placebo in LDL-C percent change from baseline was -61.9% (95% CI: -64.3%, -59.4%; p-value: <0.0001). For detailed results see Table 2. At week 12, 82.1% of patients in the alirocumab group reached an LDL-C <70 mg/dL (<1.81 mmol/L) compared to 7.2% of patients in the placebo group. Difference versus placebo was statistically significant at week 24 for all lipids/lipoproteins.

COMBO I study

A multicenter, double-blind, placebo-controlled, 52 week study included 311 patients categorised as very high CV risk and not at their pre-defined target LDL-C on a maximally tolerated dose of statin, with or without other lipid-modifying therapy. Patients received either 75 mg alirocumab Q2W or placebo in addition to their existing lipid-modifying therapy. Dose up-titration of alirocumab to 150 mg Q2W occurred at week 12 in patients with LDL-C ≥70 mg/dL (≥1.81 mmol/L). At week 24, the mean treatment difference from placebo in LDL-C percent change from baseline was -45.9% (95% CI: -52.5%, -39.3%; p-value: <0.0001). For detailed results see Table 4. At week 12 (before up-titration), 76.0% of patients in the alirocumab group reached an LDL-C of <70 mg/dL (< 1.81 mmol/L) as compared to 11.3% in the placebo group. The dose was up-titrated to 150 mg Q2W in 32 (16.8%) patients treated beyond 12 weeks. Among the subgroup of patients up-titrated at week 12, an additional 22.8% mean reduction in LDL-C was achieved at week 24. The difference versus placebo was statistically significant at week 24 for all lipids/ lipoproteins except TG and Apo A-1.

Placebo-controlled phase 3 studies (on background statin) in patients with heterozygous familial hypercholesterolaemia (heFH)

FH I and FH II studies

Two multicenter, placebo-controlled, double-blind 18-month studies included 732 patients with heFH receiving a maximally tolerated dose of statin, with or without other lipid-modifying therapy. Patients received either alirocumab 75 mg Q2W or placebo in addition to their existing lipid-modifying therapy. Dose up-titration of alirocumab to 150 mg Q2W occurred at week 12 in patients with LDL-C ≥70 mg/dL (≥1.81 mmol/L). At week 24, the mean treatment difference from placebo in LDL-C percent change from baseline was -55.8% (95% CI: -60.0%, -51.6%; p-value: < 0.0001). For detailed results see Table 2. At week 12 (before up-titration), 50.2% of patients reached an LDL-C of <70 mg/dL (<1.81 mmol/L) as compared to 0.6% in the placebo group. Among the subgroup of patients up-titrated at week 12, an additional 15.7% mean reduction in LDL-C was achieved at week 24. Difference versus placebo was statistically significant at week 24 for all lipids/ lipoproteins.

HIGH FH study

A third multicenter, double-blind, placebo-controlled 18-month study included 106 heFH patients on a maximally tolerated dose of statin, with or without other lipid-modifying therapies, and a baseline LDL-C ≥160 mg/dL (≥4.14 mmol/L). Patients received either alirocumab at a dose of 150 mg Q2W or placebo in addition to their existing lipid-modifying therapy. At week 24, the mean treatment difference from placebo in LDL-C percent change from baseline was -39.1% (95% CI: -51.1%, -27.1%; p-value: <0.0001). For detailed results see Table 2. Mean changes for all other lipids/ lipoproteins were similar to the FH I and FH II studies, however statistical significance was not reached for TG, HDL-C and Apo A-1.

Ezetimibe-controlled phase 3 study (on background statin) in patients with primary hypercholesterolaemia or mixed dyslipidaemia

COMBO II study

A multicenter, double-blind, ezetimibe-controlled 2 year study included 707 patients categorised as very high CV risk and not at their pre-defined target LDL-C on a maximally tolerated dose of statin. Patients received either alirocumab 75 mg Q2W or ezetimibe 10 mg once daily in addition to their existing statin therapy. Dose up-titration of alirocumab to 150 mg Q2W occurred at week 12 in patients with LDL-C ≥70 mg/dL (≥1.81 mmol/L). At week 24, the mean treatment difference from ezetimibe in LDL-C percent change from baseline was -29.8% (95% CI: -34.4%, -25.3%; p-value: <0.0001). For detailed results see Table 2. At week 12 (before up-titration), 77.2% of patients reached an LDL-C of <70 mg/dL (<1.81 mmol/L) as compared to 46.2% in the ezetimibe group. Among the subgroup of patients up-titrated at week 12, an additional 10.5% mean reduction in LDL-C was achieved at week 24. Difference versus ezetimibe was statistically significant at week 24 for all lipids/ lipoproteins except for TG, and Apo A-1.

Monotherapy or as add-on to non-statin lipid-modifying therapy

Ezetimibe-controlled phase 3 trials in patients with primary hypercholesterolaemia (without a background statin)

ALTERNATIVE study

A multicentre, double-blind, ezetimibe-controlled, 24 week study included 248 patients with documented statin intolerance due to skeletal muscle-related symptoms. Patients received either alirocumab 75 mg Q2W or ezetimibe 10 mg once daily, or atorvastatin 20 mg once daily (as a re-challenge arm). Dose up-titration of alirocumab to 150 mg Q2W occurred at week 12 in patients with LDL-C ≥70 mg/dL (≥1.81 mmol/L) or ≥100 mg/dL (≥2.59 mmol/L), depending on their level of CV risk. At week 24, the mean treatment difference from ezetimibe in LDL-C percent change from baseline was -30.4% (95% CI: -36.6%, -24.2%; p-value: <0.0001). For detailed results see Table 2. At week 12 (before up-titration), 34.9% of patients reached an LDL-C of <70 mg/dL (<1.81 mmol/L) as compared to 0% in the ezetimibe group. Among the subgroup of patients up-titrated at week 12, an additional 3.6% mean reduction in LDL-C was achieved at week 24. Difference versus ezetimibe was statistically significant at week 24 for LDL-C, Total-C, Non-HDL-C, Apo B, and Lp(a).

This trial evaluated patients who did not tolerate at least two statins (at least one at the lowest approved dose), In these patients, musculo-skeletal adverse events occurred at a lower rate in the alirocumab group (32.5%) as compared to the atorvastatin group (46.0%) (HR= 0.61 [95% CI, 0.38 to 0.99]), and a lower percentage of patients in the alirocumab group (15.9%) discontinued study treatment due to musculo-skeletal adverse events as compared to the atorvastatin group (22.2%). In the five placebo-controlled trials in patients on a maximally tolerated dose of statin (n=3752), the discontinuation rate due to musculo-skeletal adverse events was 0.4% in the alirocumab group and 0.5% in the placebo group.

MONO study

A multicenter, double-blind, ezetimibe-controlled, 24-week study included 103 patients with a moderate CV risk, not taking statins or other lipid-modifying therapies, and a baseline LDL-C between 100 mg/dL (2.59 mmol/L) to 190 mg/dL (4.91 mmol/L). Patients received either alirocumab 75 mg Q2W or ezetimibe 10 mg once daily. Dose up-titration of alirocumab to 150 mg Q2W occurred at week 12 in patients with LDL-C ≥70 mg/dL (≥1.81 mmol/L). At week 24, the mean treatment difference from ezetimibe in LDL-C percent change from baseline was -31.6% (95% CI: -40.2%, -23.0%; p-value: <0.0001). For detailed results see Table 2. At week 12 (before up-titration), 57.7% of patients reached an LDL-C of <70 mg/dL (<1.81 mmol/L) as compared to 0% in the ezetimibe group. The dose was up-titrated to 150 mg Q2W in 14 (30.4%) patients treated beyond 12 weeks. Among the subgroup of patients up-titrated at week 12, an additional 1.4 % mean reduction in LDL-C was achieved at week 24. The difference versus ezetimibe was statistically significant at week 24 for LDL-C, Total-C, Non-HDL-C and Apo B.

Table 2: Mean percent change from baseline in LDL-C and other lipids/ lipoproteins in placebo-controlled and ezetimibe-controlled studies – 75 mg and/or 150 mg Q2W dosing regimen

Mean Percent Change from Baseline in Placebo-Controlled Studies on Background Statin								
	LONG TERM (N=2310)		FHI and FHII (N=732)		High FH (N=106)		COMBO I (N=311)	
	Placebo	Alirocumab	Placebo	Alirocumab	Placebo	Alirocumab	Placebo	Alirocumab
Number of patients	780	1530	244	488	35	71	106	205
Mean Baseline LDL-C in mg/dL (mmol/L)	122.0 (3.16)	122.8 (3.18)	140.9 (3.65)	141.3 (3.66)	201.0 (5.21)	196.3 (5.10)	104.6 (2.71)	100.3 (2.60)
Week 12								
LDL-C (ITT)[a]	1.5	-63.3	5.4	-43.6	-6.6	-46.9	1.1	-46.3
LDL-C (on treatment)[b]	1.4	-64.2	5.3	-44.0	-6.6	-46.9	1.7	-47.6
Week 24								
LDL-C (ITT)[a]	0.8	-61.0[c]	7.1	-48.8[d]	-6.6	-45.7[e]	-2.3	-48.2[f]
LDL-C (on treatment)[b]	0.7	-62.8	6.8	-49.3	-6.6	-45.5	-0.8	-50.7
Non-HDL-C	0.7	-51.6	7.4	-42.8	-6.2	-41.9	-1.6	-39.1
Apo B	1.2	-52.8	1.9	-41.7	-8.7	-39.0	-0.9	-36.7
Total-C	-0.3	-37.8	5.5	-31.2	-4.8	-33.2	-2.9	-27.9
Lp(a)	-3.7	-29.3	-8.5	-26.9	-8.7	-23.5	-5.9	-20.5
TG	1.8	-15.6	4.3	-9.8	-1.9	-10.5	-5.4	-6.0
HDL-C	-0.6	4.0	0.2	7.8	3.9	7.5	-3.8	3.5
Apo A-1	1.2	4.0	-0.4	4.2	2.0	5.6	-2.5	3.3

Mean percent change from baseline in ezetimibe-controlled studies						
	On background statin		Without background statin			
	COMBO II (N=707)		ALTERNATIVE (N=248)		MONO (N=103)	
	Ezetimibe	Alirocumab	Ezetimibe	Alirocumab	Ezetimibe	Alirocumab
Number of patients	240	467	122	126	51	52
Mean baseline LDL-C in mg/dL (mmol/L)	104.5 (2.71)	108.3 (2.81)	194.2 (5.03)	191.1 (5.0)	138.3 (3.58)	141.1 (3.65)
Week 12						
LDL-C (ITT)[a]	-21.8	-51.2	-15.6	-47.0	-19.6	-48.1
LDL-C (on treatment)[b]	-22.7	-52.4	-18.0	-51.2	-20.4	-53.2
Week24						
LDL-C (ITT)[a]	-20.7	-50.6[g]	-14.6	-45.0[h]	-15.6	-47.2[i]
LDL-C (on treatment)[b]	-21.8	-52.4	-17.1	-52.2	-17.2	-54.1

Non-HDL-C	-19.2	-42.1	-14.6	-40.2	-15.1	-40.6
Apo B	-18.3	-40.7	-11.2	-36.3	-11.0	-36.7
Total-C	-14.6	-29.3	-10.9	-31.8	-10.9	-29.6
Lp(a)	-6.1	-27.8	-7.3	-25.9	-12.3	-16.7
TG	-12.8	-13.0	-3.6	-9.3	-10.8	-11.9
HDL-C	0.5	8.6	6.8	7.7	1.6	6.0
Apo A-1	-1.3	5.0	2.9	4.8	-0.6	4.7

[a] ITT analysis – intent-to-treat population, includes all lipid data throughout the duration of the study irrespective of adherence to the study treatment.
[b] On-treatment analysis – analysis restricted to the time period that patients actually received treatment.
The % LDL-C reduction at week 24 corresponds to a mean absolute change of:
[c] -74.2 mg/dL (-1.92 mmol/L); [d] -71.1 mg/dL (-1.84 mmol/L); [e] -90.8 mg/dL (-2.35 mmol/L); [f] -50.3 mg/dL (-1.30 mmol/L); [g] -55.4 mg/dL (1.44 mmol/L); [h] -84.2 mg/dL (-2.18 mmol/L); [i] -66.9 mg/dL (-1.73 mmol/L)

Every 4 week (Q4W) dosing regimen

CHOICE I study

A multicenter, double-blind, placebo-controlled, 48 week study included 540 patients on a maximally tolerated dose of a statin, with or without other lipid-modifying therapy (308 in the alirocumab 300 mg Q4W group, 76 in the alirocumab 75 mg Q2W group, and 156 in the placebo group), and 252 patients not treated with a statin (144 in the alirocumab 300 mg Q4W group, 37 in the alirocumab 75 mg Q2W group, and 71 in the placebo group). Patients received either alirocumab 300 mg Q4W, alirocumab 75 mg Q2W, or placebo in addition to their existing lipid-modifying therapy (statin, non-statin therapy or diet alone). Patients in the alirocumab 300 mg every 4 weeks treatment group received alternating placebo injections to maintain blinding in regard to injection frequency. Overall, 71.6% of patients were categorized at high or very high CV risk and not at their LDL-C target. Dose adjustment in the alirocumab groups to 150 mg Q2W occurred at week 12 in patients with LDL-C ≥70 mg/dL or ≥100 mg/dL, depending on their level of CV risk, or in patients who did not have at least a 30% reduction of LDL-C from baseline.

In the cohort of patients on background statin, the mean baseline LDL-C was 112.7 mg/dL. At week 12, the mean percent change from baseline with alirocumab 300 mg Q4W in LDL-C (ITT analysis) was -55.3% compared to +1.1% for placebo. At week 12 (before dose adjustment), 77.3% of patients treated with alirocumab 300 mg Q4W reached an LDL-C of <70 mg/dL as compared to 9.3% in the placebo group. At week 24, the mean percent change from baseline with alirocumab 300 mg Q4W/150 mg Q2W in LDL-C (ITT analysis) was -58.8% compared to -0.1% for placebo. At week 24, the mean treatment difference for alirocumab 300 mg Q4W/150 mg Q2W from placebo in LDL-C percent change from baseline was -58.7% (97.5% CI: -65.0%, -52.4%; p-value: < 0.0001). In patients treated beyond 12 weeks, the dose was adjusted to 150 mg Q2W in 56 (19.3%) of 290 patients in the alirocumab 300 mg Q4W arm. Among the subgroup of patients dose adjusted to 150 mg Q2W at week 12, an additional 25.4% reduction in LDL-C was achieved at week 24.

In the cohort of patients not treated with a concomitant statin, the mean baseline LDL-C was 142.1 mg/dL. At week 12, the mean percent change from baseline with alirocumab 300 mg Q4W in LDL-C (ITT analysis) was -58.4% compared to +0.3% for placebo. At week 12 (before dose adjustment), 65.2% of patients treated with alirocumab 300 mg Q4W reached an LDL-C of <70 mg/dL as compared to 2.8% in the placebo group. At week 24, the mean percent change from baseline with alirocumab 300 mg Q4W/150 mg Q2W in LDL-C (ITT analysis) was -52.7% compared to -0.3% for placebo. At week 24, the mean treatment difference for alirocumab 300 mg Q4W/150 mg Q2W from placebo in LDL-C percent change from baseline was -52.4% (97.5% CI: -59.8%, -45.0%; p-value: < 0.0001). In patients treated beyond 12 weeks, the dose was adjusted to 150 mg Q2W in 19 (14.7%) of 129 patients in the alirocumab 300 mg Q4W arm. Among the subgroup of patients dose adjusted to 150 mg Q2W at week 12, an additional 7.3% mean reduction in LDL-C was achieved at week 24.

In both cohorts, the difference vs placebo was statistically significant at week 24 for all lipid parameters, except for Apo A-1 in the subgroup of patients on background statin.

Clinical efficacy and safety in prevention of cardiovascular events

ODYSSEY OUTCOMES study

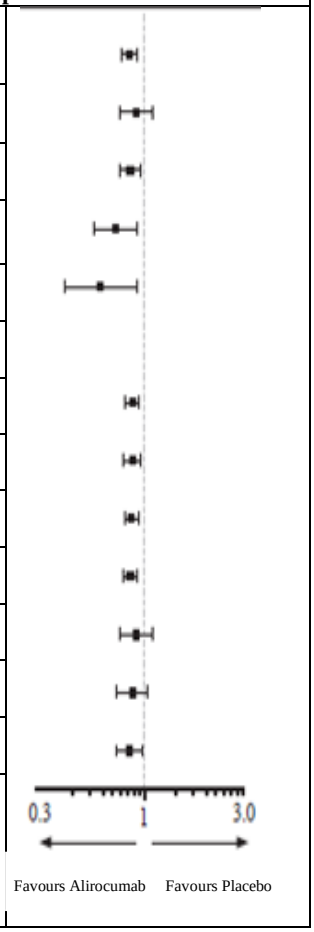
A multicentre, double-blind, placebo-controlled trial included 18,924 adult patients (9,462 alirocumab; 9,462 placebo) followed for up to 5 years. Patients had experienced an acute coronary syndrome (ACS) event 4 to 52 weeks prior to randomization and were treated with a lipid-modifying-therapy (LMT) regimen that was statin-intensive (defined as atorvastatin 40 or 80 mg, or rosuvastatin 20 or 40 mg) or at maximally tolerated dose of those statins, with or without other LMT. Patients were randomized 1:1 to receive either alirocumab 75 mg once every two weeks (Q2W) or placebo Q2W. At month 2, if additional LDL-C lowering was required based on pre-specified LDL-C criteria (LDL-C ≥50 mg/dL or 1.29 mmol/L), alirocumab was adjusted to 150 mg Q2W. For patients who had their dose adjusted to 150 mg Q2W and who had two consecutive LDL-C values below 25 mg/dL (0.65 mmol/L), down-titration from 150 mg Q2W to 75 mg Q2W was performed. Patients on 75 mg Q2W who had two consecutive LDL-C values below 15 mg/dL (0.39 mmol/L) were switched to placebo in a blinded fashion. Approximately 2,615 (27.7%) of 9,451 patients treated with alirocumab required dose adjustment to 150 mg Q2W. Of these 2615 patients, 805 (30.8%) were down-titrated to 75 mg Q2W. Overall, 730 (7.7%) of 9,451 patients switched to placebo. A total of 99.5% of patients were followed for survival until the end of the trial. The median follow-up duration was 33 months.

The index ACS event was a myocardial infarction in 83.2% of patients (34.6% STEMI, 48.6% NSTEMI) and an episode of unstable angina in 16.8% of patients. Most patients (88.8%) were receiving high intensity statin therapy with or without other LMT at randomization. The mean LDL-C value at baseline was 92.4 mg/dL (2.39 mmol/L).

Alirocumab significantly reduced the risk for the primary composite endpoint of the time to first occurrence of Major Adverse Cardiovascular Events (MACE-plus) consisting of coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), fatal and non-fatal ischemic stroke, or unstable angina (UA) requiring hospitalization (HR 0.85, 95% CI: 0.78, 0.93; p-value=0.0003). Alirocumab also significantly reduced the following composite endpoints: risk of CHD event; major CHD event; cardiovascular event; and the composite of all-cause mortality, non-fatal MI, and non-fatal ischemic stroke. A reduction of all-cause mortality was also observed, with only nominal statistical significance by hierarchical testing (HR 0.85, 95% CI: 0.73, 0.98). The results are presented in Table 3.

Table 3: Efficacy of alirocumab in ODYSSEY OUTCOMES (overall population)

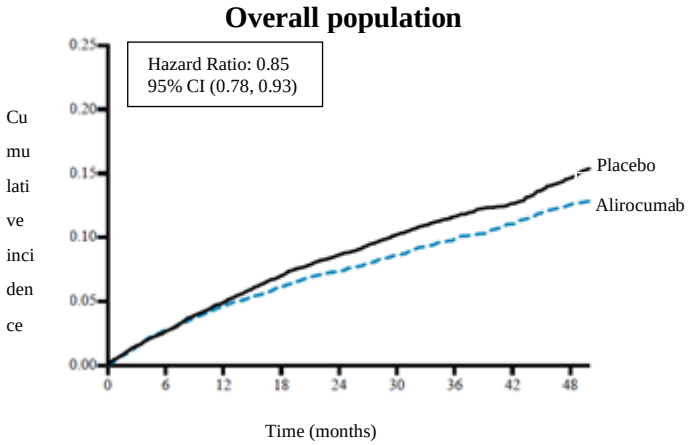
Endpoint	Number of events		Hazard ratio (95% CI) p-value
	Alirocumab N=9,462 n (%)	Placebo N=9,462 n (%)	
Primary endpoint (MACE-plus[a])	903 (9.5%)	1052 (11.1%)	0.85 (0.78, 0.93) 0.0003
CHD death	205 (2.2%)	222 (2.3%)	0.92 (0.76, 1.11) 0.38
Non-fatal MI	626 (6.6%)	722 (7.6%)	0.86 (0.77, 0.96) 0.006[f]
Ischemic stroke	111 (1.2%)	152 (1.6%)	0.73 (0.57, 0.93) 0.01[f]
Unstable angina[b]	37 (0.4%)	60 (0.6%)	0.61 (0.41, 0.92) 0.02[f]
Secondary endpoints			
CHD event[c]	1199 (12.7%)	1349 (14.3%)	0.88 (0.81, 0.95) 0.0013
Major CHD event[d]	793 (8.4%)	899 (9.5%)	0.88 (0.80, 0.96) 0.0060
Cardiovascular event[e]	1301 (13.7%)	1474 (15.6%)	0.87 (0.81, 0.94) 0.0003
All-cause mortality, non-fatal MI, non-fatal ischemic stroke	973 (10.3%)	1126 (11.9%)	0.86 (0.79, 0.93) 0.0003
CHD death	205 (2.2%)	222 (2.3%)	0.92 (0.76, 1.11) 0.3824
CV death	240 (2.5%)	271 (2.9%)	0.88 (0.74, 1.05) 0.1528
All-cause mortality	334 (3.5%)	392 (4.1%)	0.85 (0.73, 0.98) 0.0261[f]



[a] MACE-plus defined as a composite of: coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), fatal and non-fatal ischemic stroke, or unstable angina (UA) requiring hospitalization
[b] Unstable angina requiring hospitalization
[c] CHD event defined as: major CHD event[d], unstable angina requiring hospitalization, ischemia-driven coronary revascularization procedure
[d] Major CHD event defined as: CHD death, non-fatal MI
[e] Cardiovascular event defined as follows: CV death, any non-fatal CHD event, and non-fatal ischemic stroke
[f] Nominal significance

The Kaplan-Meier estimates of the cumulative incidence of the primary endpoint for the overall patient population over time are presented in Figure 1.

Figure 1 Primary composite endpoint cumulative incidence over 4 years in ODYSSEY OUTCOMES



Neurocognitive function

A 96 week, randomized, double-blinded, placebo-controlled trial evaluated the effect of alirocumab on neurocognitive function after 96 weeks of treatment (~2 years) in patients with heterozygous familial hypercholesterolemia (HeFH) or non-familial hypercholesterolemia at high or very high cardiovascular risk.

Neurocognitive function was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB). A total of 2171 patients were randomized; 1087 patients were treated with alirocumab 75 mg and/or 150 mg every 2 weeks and 1084 patients were treated with placebo. A majority (>80%) of patients in each group completed the 96-week, double-blind treatment period.

Over the 96 weeks of treatment, alirocumab showed no effect on neurocognitive function. The percentage of patients who experienced neurocognitive disorders was low in the alirocumab (1.3%) treatment groups and comparable to placebo (1.7%). No safety concerns related to neurocognitive function were observed in patients treated with alirocumab who experienced either 2 consecutive LDL-C values <25 mg/dL (<0.65 mmol/L) or <15 mg/dL (<0.39 mmol/L) during the treatment period.

Paediatric population

A 48-week, open-label study was conducted to evaluate the efficacy and safety of alirocumab 75 mg Q2W (if body weight (BW) < 50 kg) or 150 mg Q2W (if BW ≥ 50 kg) in 18 paediatric patients (8 to 17 years of age) with HoFH on top of background treatments. Patients received alirocumab 75 or 150 mg Q2W without dose adjustment up to week 12.

The mean baseline LDL-C was 9.6 mmol/l (373 mg/dL). The mean percent change from baseline in LDL-C to week 12 was -4.1% (95% CI: -23.1% to 14.9%) in the ITT population (N=18) and was associated with a high variability in the response with regard to the decrease in LDL-C. Responders achieving ≥15% reduction from baseline at weeks 12, 24, and 48 were 50%, 50% and 39% respectively (see section 4.2).

The European Medicines Agency has deferred the obligation to submit the results of studies with Praluent in one or more subsets of the paediatric population in the treatment of elevated cholesterol (see section 4.2 for information on paediatric use).

The European Medicines Agency has waived the obligation to submit the results of studies with Praluent in all subsets of the paediatric population in the treatment of mixed dyslipidaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

After subcutaneous administration of 50 mg to 300 mg alirocumab, median times to maximum serum concentration (t_{max}) were 3-7 days. The pharmacokinetics of alirocumab after single subcutaneous administration of 75 mg into the abdomen, upper arm or thigh were similar. The absolute bioavailability of alirocumab after subcutaneous administration was about 85% as determined by population pharmacokinetic analysis. Monthly exposure with 300 mg every 4 weeks treatment was similar to that of 150 mg every 2 weeks. The fluctuations between C_{max} and C_{trough} were higher for the every 4 weeks dosage regimen. Steady state was reached after 2 to 3 doses with an accumulation ratio up to a maximum of about 2-fold.

Distribution

Following intravenous administration, the volume of distribution was about 0.04 to 0.05 L/kg indicating that alirocumab is distributed primarily in the circulatory system.

Biotransformation

Specific metabolism studies were not conducted, because alirocumab is a protein. Alirocumab is expected to degrade to small peptides and individual amino acids.

Elimination

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 as monotherapy at subcutaneous doses of either 75 mg Q2W or 150 mg Q2W. When co-administered with a statin, the median apparent half-life of alirocumab was 12 days.

Linearity/non-linearity

A slightly greater than dose proportional increase was observed, with a 2.1- to 2.7-fold increase in total alirocumab concentrations for a 2-fold increase in dose from 75 mg to 150 mg Q2W.

Special populations

Elderly

Based on a population pharmacokinetic analysis, age was associated with a small difference in alirocumab exposure at steady state, with no impact on efficacy or safety.

Gender

Based on a population pharmacokinetic analysis, gender has no impact on alirocumab pharmacokinetics.

Race

Based on a population pharmacokinetic analysis, race had no impact on alirocumab pharmacokinetics. Following single-dose subcutaneous administration of 100 mg to 300 mg alirocumab, there was no meaningful difference in exposure between Japanese and Caucasian healthy subjects.

Body weight

Body weight was identified as one significant covariate in the final population PK model impacting alirocumab pharmacokinetics. Alirocumab exposure (AUC_{0-14d}) at steady state at both the 75 and 150 mg

Q2W dosing regimen was decreased by 29% and 36% in patients weighing more than 100 kg as compared to patients weighing between 50 kg and 100 kg. This did not translate into a clinically meaningful difference in LDL-C lowering.

Hepatic impairment

In a phase 1 study, after administration of a single 75 mg subcutaneous dose, alirocumab pharmacokinetic profiles in subjects with mild and moderate hepatic impairment were similar as compared to subjects with normal hepatic function. No data are available in patients with severe hepatic impairment.

Renal impairment

Since monoclonal antibodies are not known to be eliminated via renal pathways, renal function is not expected to impact the pharmacokinetics of alirocumab. Population pharmacokinetic analyses showed that alirocumab exposure (AUC0-14d) at steady state at both the 75 and 150 mg Q2W dosing regimen was increased by 22%-35%, and 49%-50% in patients with mild and moderate renal impairment, respectively, compared to patients with normal renal function. The distribution of body weight and age, two covariates impacting alirocumab exposure, were different among renal function categories and most likely explain the observed pharmacokinetic differences. Limited data are available in patients with severe renal impairment; in these patients the exposure to alirocumab was approximately 2-fold higher compared with subjects with normal renal function.

Paediatric population

Limited pharmacokinetic data are available in 18 paediatric patients (8 to 17 years of age) with HoFH. The steady-state mean C_{trough} alirocumab concentrations was reached at or before Week 12 in both alirocumab 75 mg Q2W and 150 mg Q2W groups. No studies with alirocumab have been performed in paediatric patients less than 8 years of age (see section 5.1).

Pharmacokinetic/pharmacodynamic relationship(s)

The pharmacodynamic effect of alirocumab in lowering LDL-C is indirect, and mediated through the binding to PCSK9. A concentration-dependent reduction in free PCSK9 and LDL-C is observed until target saturation is achieved. Upon saturation of PCSK9 binding, further increases in alirocumab concentrations do not result in a further LDL-C reduction, however an extended duration of the LDL-C lowering effect is observed.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

Reproductive toxicology studies in rats and monkeys indicated that alirocumab, like other IgG antibodies, crosses the placental barrier.

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 monkeys, and no alirocumab-related anatomic pathology or histopathology findings in reproductive tissues in any rat or monkey toxicology study.

There were no adverse effects on foetal growth or development in rats or monkeys. Maternal toxicity was not evident in pregnant monkeys at systemic exposures that were 81 times the human exposure at the 150 mg Q2W dose. However, maternal toxicity was noted in pregnant rats at systemic exposures estimated to be approximately 5.3 times greater than the human exposure at the 150 mg Q2W dose (based on exposure measured in non-pregnant rats during a 5-week toxicology study).

The offspring of monkeys that received high doses of alirocumab weekly throughout pregnancy had a weaker secondary immune response to antigen challenge than did the offspring of control animals. There was no other evidence of alirocumab-related immune dysfunction in the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Sucrose
Polysorbate 20
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Praluent 75 mg solution for injection in pre-filled pen

3 years.

Praluent 75 mg solution for injection in pre-filled syringe

3 years.

Praluent 150 mg solution for injection in pre-filled pen

2 years.

Praluent 150 mg solution for injection in pre-filled syringe

2 years.

Praluent 300 mg solution for injection in pre-filled pen

2 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C). Do not freeze.
Praluent can be stored outside the refrigerator (below 25 °C) protected from light for a single period not exceeding 30 days. After removal from the refrigerator, the medicinal product must be used within 30 days or discarded.

Keep the pen or syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container

1 ml or 2 ml solution in a siliconised Type 1 clear glass syringe, equipped with a stainless steel staked needle, a styrene-butadiene rubber needle shield, and an ethylene tetrafluoroethylene -coated bromobutyl rubber plunger stopper.

75 mg solution for injection in pre-filled pen

The syringe components are assembled into a single-use pre-filled pen with a blue cap and a light green activation button.

Pack size:
1, 2 or 6 pre-filled pens.

Or

The syringe components are assembled into a single-use pre-filled pen with a blue cap and without activation button.

Pack size:
1, 2 or 6 pre-filled pens without activation button.

150 mg solution for injection in pre-filled pen

The syringe components are assembled into a single-use pre-filled pen with a blue cap and a dark grey activation button.

Pack size:
1, 2 or 6 pre-filled pens.

Or

The syringe components are assembled into a single-use pre-filled pen with a blue cap and without activation button.

Pack size:
1, 2 or 6 pre-filled pens without activation button.

300 mg solution for injection in pre-filled pen

The syringe components are assembled into a single-use pre-filled pen with a blue cap and without activation button.

Pack size:
1 or 3 pre-filled pens without activation button.

75 mg solution for injection in pre-filled syringe

The syringe is equipped with a light green polypropylene plunger rod.

Pack size:
1, 2 or 6 pre-filled syringes.

150 mg solution for injection in pre-filled syringe

The syringe is equipped with a dark grey polypropylene plunger rod.

Pack size:
1, 2 or 6 pre-filled syringes.

Not all presentations and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

After use, the pre-filled pen/ pre-filled syringe should be placed into a puncture resistant container. The container should not be recycled.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1031/001
EU/1/15/1031/002
EU/1/15/1031/003
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EU/1/15/1031/019
EU/1/15/1031/020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 September 2015
Date of latest renewal: 2 June 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Regeneron Pharmaceuticals, Inc.
81 Columbia Turnpike
Rensselaer, NY 12144
United States

Regeneron Ireland DAC
Raheen Business Park
Limerick
Ireland

SANOFI CHIMIE
9 Quai Jules Guesde
94403 Vitry-sur-Seine
France

Name and address of the manufacturers responsible for batch release

For pre-filled syringes
Sanofi Winthrop Industrie
1051 Boulevard Industriel
76580 Le Trait
France

For pre-filled pens
Sanofi-Aventis Deutschland GmbH
Industriepark Hoechst
Brüningstraße 50
65926 Frankfurt am Main
Germany

Or

Genzyme Ireland Ltd
IDA Industrial Park
Old Kilmeaden Road
Waterford
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – Pre-filled pen 75 mg

1. NAME OF THE MEDICINAL PRODUCT

Praluent 75 mg solution for injection in pre-filled pen
alirocumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 75 mg alirocumab in 1 ml solution.

3. LIST OF EXCIPIENTS

Excipients: histidine, sucrose, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen
2 pre-filled pens
6 pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use.
Subcutaneous use
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Can be stored outside the refrigerator below 25 °C for a single period up to 30 days protected from light.
Keep the pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1031/001 1 pre-filled pen
EU/1/15/1031/002 2 pre-filled pens
EU/1/15/1031/003 6 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Praluent 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – Pre-filled pen 75 mg (without activation button)

1. NAME OF THE MEDICINAL PRODUCT

Praluent 75 mg solution for injection in pre-filled pen
alirocumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 75 mg alirocumab in 1 ml solution.

3. LIST OF EXCIPIENTS

Excipients: histidine, sucrose, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen without activation button
2 pre-filled pens without activation button
6 pre-filled pens without activation button

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use.
Subcutaneous use
Open here

1 pre-filled pen without activation button
2 pre-filled pens without activation button
6 pre-filled pens without activation button
Read “Instructions for use” leaflet before using the pen

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Can be stored outside the refrigerator below 25 °C for a single period up to 30 days protected from light.
Keep the pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1031/013 1 pre-filled pen
EU/1/15/1031/014 2 pre-filled pen
EU/1/15/1031/015 6 pre-filled pen

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Praluent 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL – 75 mg
PEN LABEL – 75 mg (without activation button)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Praluent 75 mg injection
alirocumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – Pre-filled pen 150 mg

1. NAME OF THE MEDICINAL PRODUCT

Praluent 150 mg solution for injection in pre-filled pen
alirocumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 150 mg alirocumab in 1 ml solution.

3. LIST OF EXCIPIENTS

Excipients: histidine, sucrose, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen
2 pre-filled pens
6 pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use.
Subcutaneous use
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Can be stored outside the refrigerator below 25 °C for a single period up to 30 days protected from light.
Keep the pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1031/007 1 pre-filled pen
EU/1/15/1031/008 2 pre-filled pens
EU/1/15/1031/009 6 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Praluent 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – Pre-filled pen 150 mg (without activation button)

1. NAME OF THE MEDICINAL PRODUCT

Praluent 150 mg solution for injection in pre-filled pen
alirocumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 150 mg alirocumab in 1 ml solution.

3. LIST OF EXCIPIENTS

Excipients: histidine, sucrose, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen without activation button
2 pre-filled pens without activation button
6 pre-filled pens without activation button

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use.
Subcutaneous use
Open here

1 pre-filled pen without activation button
2 pre-filled pens without activation button
6 pre-filled pens without activation button
Read “Instructions for use” leaflet before using the pen

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Can be stored outside the refrigerator below 25 °C for a single period up to 30 days protected from light.
Keep the pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1031/016 1 pre-filled pens
EU/1/15/1031/017 2 pre-filled pens
EU/1/15/1031/018 6 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Praluent 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL – 150 mg
PEN LABEL – 150 mg (without activation button)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Praluent 150 mg injection
alirocumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – Pre-filled pen 300 mg

1. NAME OF THE MEDICINAL PRODUCT

Praluent 300 mg solution for injection in pre-filled pen
alirocumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 300 mg alirocumab in 2 ml solution.

3. LIST OF EXCIPIENTS

Excipients: histidine, sucrose, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen without activation button
3 pre-filled pens without activation button

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use.
Subcutaneous use
Open here

1 pre-filled pen without activation button
3 pre-filled pens without activation button
Read “Instructions for use” leaflet before using the pen

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Can be stored outside the refrigerator below 25 °C for a single period up to 30 days protected from light.
Keep the pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1031/019 1 pre-filled pen
EU/1/15/1031/020 3 pre-filled pen

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Praluent 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL – 300 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Praluent 300 mg injection
alirocumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 mg/ml
2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – Pre-filled syringe 75 mg

1. NAME OF THE MEDICINAL PRODUCT

Praluent 75 mg solution for injection in pre-filled syringe
alirocumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 75 mg alirocumab in 1 ml solution.

3. LIST OF EXCIPIENTS

Excipients: histidine, sucrose, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe
2 pre-filled syringes
6 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Can be stored outside the refrigerator below 25 °C for a single period up to 30 days protected from light.
Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1031/004 1 pre-filled syringe
EU/1/15/1031/005 2 pre-filled syringes
EU/1/15/1031/006 6 pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Praluent 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER – Pre-filled syringe 75 mg

1. NAME OF THE MEDICINAL PRODUCT

Praluent 75 mg solution for injection in pre-filled syringe
alirocumab

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL – 75 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Praluent 75 mg injection
alirocumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – Pre-filled syringe 150 mg

1. NAME OF THE MEDICINAL PRODUCT

Praluent 150 mg solution for injection in pre-filled syringe
alirocumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 150 mg alirocumab in 1 ml solution.

3. LIST OF EXCIPIENTS

Excipients: histidine, sucrose, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe
2 pre-filled syringes
6 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Can be stored outside the refrigerator below 25 °C for a single period up to 30 days protected from light.
Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1031/010 1 pre-filled syringe
EU/1/15/1031/011 2 pre-filled syringes
EU/1/15/1031/012 6 pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Praluent 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER – Pre-filled syringe 150 mg

1. NAME OF THE MEDICINAL PRODUCT

Praluent 150 mg solution for injection in pre-filled syringe
alirocumab

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL – 150 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Praluent 150 mg injection
alirocumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Praluent 75 mg solution for injection in a pre-filled pen
Praluent 150 mg solution for injection in a pre-filled pen
Praluent 300 mg solution for injection in a pre-filled pen
alirocumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Praluent is and what it is used for

What Praluent is
- Praluent contains the active substance alirocumab.
- Praluent is a monoclonal antibody (a type of specialised protein designed to attach to a target substance in the body). Monoclonal antibodies are proteins that recognise and bind to other unique proteins. Alirocumab binds to PCSK9.

How Praluent works
Praluent helps lower your levels of "bad" cholesterol (also called "LDL cholesterol"). Praluent blocks a protein called PCSK9.
- PCSK9 is a protein secreted by liver cells.
- "Bad" cholesterol is normally removed from your blood by binding to specific "receptors" (docking stations) in your liver.
- PCSK9 lowers the number of these receptors in the liver – this causes your "bad" cholesterol to be higher than it should.
- By blocking PCSK9, Praluent increases the number of receptors available to help remove the "bad" cholesterol – this lowers your "bad" cholesterol levels.

What Praluent is used for
- Adults with high cholesterol levels in their blood (hypercholesterolaemia [heterozygous familial and non-familial] or mixed dyslipidaemia).
- Adults with high cholesterol levels in their blood and with cardiovascular disease to reduce cardiovascular risk.

It is given:
- together with a statin (a commonly used medicine that treats high cholesterol) or other cholesterol lowering medicines, if the maximum dose of a statin does not lower levels of cholesterol sufficiently or,
- alone or together with other cholesterol lowering medicines when statins are not tolerated or cannot be used.

Continue to follow your cholesterol-lowering diet while taking this medicine.

2. What you need to know before you use Praluent

Do not use Praluent
- if you are allergic to alirocumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Praluent.

If you develop a serious allergic reaction, stop using Praluent, talk to your doctor right away. Sometimes serious allergic reactions such as hypersensitivity, including angioedema (difficulties breathing, or swelling of the face, lips, throat or tongue), nummular eczema (reddish skin spots sometimes with blisters), and hypersensitivity vasculitis (which is a specific form of a hypersensitivity reaction with symptoms such as diarrhoea, with a rash, or purple-coloured skin spots on the skin) have occurred. For allergic reactions that may occur while taking Praluent, see section 4.

Tell your doctor if you have kidney or liver disease before using this medicine, because Praluent has been studied in few patients with severe kidney disease and not in patients with severe liver disease.

Children and adolescents
Praluent should not be given to children and adolescents under 18 years old because there is limited experience of using the medicine in these age groups.

Other medicines and Praluent
Tell your doctor, pharmacist or nurse if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.
Praluent is not recommended during pregnancy or breast-feeding.

Driving and using machines
This medicine is not expected to have any effect on your ability to drive or use machines.

3. How to use Praluent

Always use this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to inject
Your doctor will tell you which dose is right for you and how often to inject (75 mg or 150 mg once every 2 weeks, or 300 mg once every 4 weeks/monthly)). Your doctor will check your cholesterol levels and may adjust the dose (up or down) during treatment.
Always check the label of your pen to make sure you have the right medicine and the right strength.

When to inject
Inject Praluent once every 2 weeks (for the 75 mg or 150 mg dose), or once every 4 weeks/monthly (for the 300 mg dose). To give the 300 mg dose, one 300 mg injection or two 150 mg injections should be given in a row at two different injection sites.

Before you inject
Praluent should be allowed to warm to room temperature prior to use.
Read the detailed instructions for use leaflet before you inject Praluent.

Where to inject
Praluent is injected under your skin into the thigh, abdomen or upper arm.
Read the detailed instructions for use leaflet on where to inject.

Learning how to use the pre-filled pen
Before you use the pen for the first time, your doctor, pharmacist or nurse will show you how to inject Praluent.

- Always read the **"Instructions for Use"** provided in the box.
- Always use the pen as described in the **"Instructions for Use".**

If you use more Praluent than you should
If you use more Praluent than you should, talk to your doctor, pharmacist or nurse.

If you forget to use Praluent
If you miss a dose of Praluent, inject your missed dose as soon as you can. Then take your next dose at your regular scheduled time. This will keep you on the original schedule. If you are not sure when to inject Praluent, call your doctor, pharmacist or nurse.

If you stop using Praluent
Do not stop using Praluent without talking with your doctor. If you stop using Praluent, your cholesterol levels can increase.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you develop a serious allergic reaction, stop using Praluent, talk to your doctor right away. Sometimes serious allergic reactions such as hypersensitivity (difficulties breathing), nummular eczema (reddish skin spots sometimes with blisters), and hypersensitivity vasculitis (which is a specific form of a hypersensitivity reaction with symptoms such as diarrhoea, with a rash, or purple-coloured skin spots on the skin) have occurred (may affect up to 1 in 1,000 people).

Other side effects are:

Common (may affect up to 1 in 10 people)

- redness, itching, swelling, pain/tenderness where the medicine was injected (local injection site reactions)
- upper respiratory tract signs or symptoms such as sore throat, running nose, sneezing
- itching (pruritus).

Rare (may affect up to 1 in 1,000 people)

- red and itchy raised bumps or hives (urticaria)

Not Known

The following side effects have been reported since the marketing of Praluent, but how often they occur is not known:

- flu-like illness
- difficulties breathing, or swelling of the face, lips, throat or tongue (angioedema)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Praluent

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C). Do not freeze.
Keep the pen in the outer carton in order to protect from light.

If needed, individual pre-filled pens may be kept outside the refrigerator below 25°C for a maximum of 30 days. Protect from light. After removal from the refrigerator, Praluent must be used within 30 days or discarded.

Do not use this medicine if it looks discoloured or cloudy, or if it contains visible flakes or particles.

After use put the pen into a puncture-resistant container. Ask your doctor, pharmacist or nurse how to throw away the container. Do not recycle the container.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Praluent contains
- The active substance is alirocumab.

  Praluent 75 mg solution for injection in pre-filled pen
  Each pre-filled pen contains 75 milligrams of alirocumab.

  Praluent 150 mg solution for injection in pre-filled pen
  Each pre-filled pen contains 150 milligrams of alirocumab.

  Praluent 300 mg solution for injection in pre-filled pen
  Each pre-filled pen contains 300 milligrams of alirocumab.

- The other ingredients are histidine, sucrose, polysorbate 20 and water for injections.

What Praluent looks like and contents of the pack
Praluent is a clear, colourless to pale yellow solution for injection that comes in a pre-filled pen.

Praluent 75 mg solution for injection in pre-filled pen
Each pre-filled pen with green button contains 1 ml of solution, delivering one single dose of 75 milligrams of alirocumab.
It is available in pack size of 1, 2 or 6 pre-filled pens.

Each pre-filled pen without activation button contains 1 ml of solution, delivering one single dose of 75 milligrams.
It is available in pack size of 1, 2 or 6 pre-filled pens without activation button.

Praluent 150 mg solution for injection in pre-filled pen
Each pre-filled pen with grey button contains 1 ml of solution, delivering one single dose of 150 milligrams of alirocumab.
It is available in pack size of 1, 2 or 6 pre-filled pens.

Each pre-filled pen without activation button contains 1 ml of solution, delivering one single dose of 150 milligrams.
It is available in pack size of 1, 2 or 6 pre-filled pens without activation button.

Praluent 300mg solution for injection in pre-filled pen
Each pre-filled pen without activation button contains 2 ml of solution, delivering one single dose of 300 milligrams.
It is available in pack size of 1 or 3 pre-filled pens without activation button.

Not all presentations and pack sizes may be marketed.

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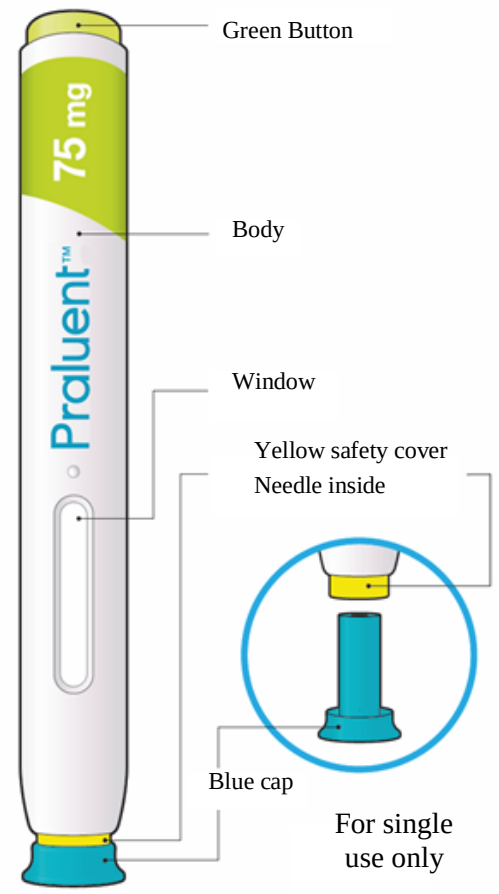
This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/

Praluent pre-filled pen

Instructions for use

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



Important information

- The medicine is injected under your skin and can be given by yourself or someone else (caregiver).
- This pen can only be used for one single injection, and must be thrown away after use.

Do

✓ Keep the Praluent pen out of the sight and reach of children.
✓ Read all of the instructions carefully before using the Praluent pen.
✓ Follow these instructions every time you use a Praluent pen.

Do not

× 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.
× Do not shake the pen.
× Do not freeze the pen.
× Do not expose the pen to direct sunlight.

Keep this leaflet. If you have questions, ask your doctor, pharmacist or nurse or call the local representative of the Marketing Authorization Holder on the package leaflet.

STEP A: Getting ready for an injection

Before you start you will need:

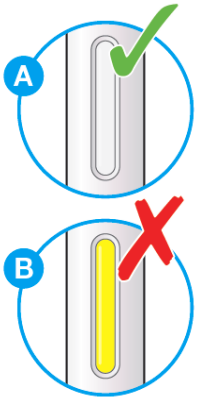
- the Praluent pen
- alcohol wipes
- cotton ball or gauze
- a puncture-resistant container (see Step B, 8).

① Look at the label on the pen.

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

② Look at the window.

- Check the liquid is clear, colourless to pale yellow and free from particles - if not, do not use (see picture A).
- You may see an air bubble. This is normal.
- Do not use if the window appears solid yellow (see picture B).



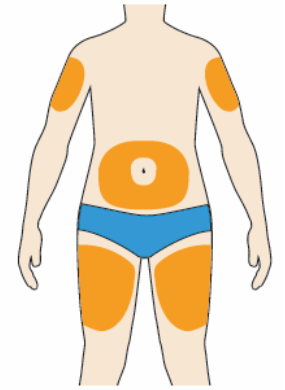
③ Let the pen warm up at room temperature for 30 to 40 minutes.

- Do not heat the pen, let it warm up on its own.
- Do not put the pen back in the refrigerator.

④ Prepare the injection site.

- Wash your hands with soap and water and dry with a towel.
- You can inject into your:
    - thigh
    - belly (except for the 5 cm area around your navel)
    - outer side of your upper arm

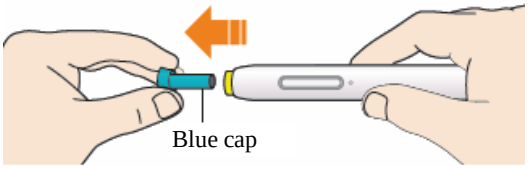
  (See picture).
- You can stand or sit to give yourself an injection.
- Clean skin in the injection area with an alcohol wipe.
- Do not use skin that is tender, hard, red or hot.
- Do not use any area near a visible vein.
- Use a different spot each time you inject.
- Do not inject Praluent with other injectable medicines at the same spot.



STEP B: How to inject

① After completing all steps in "Step A: Getting ready for an injection", pull off the blue cap

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

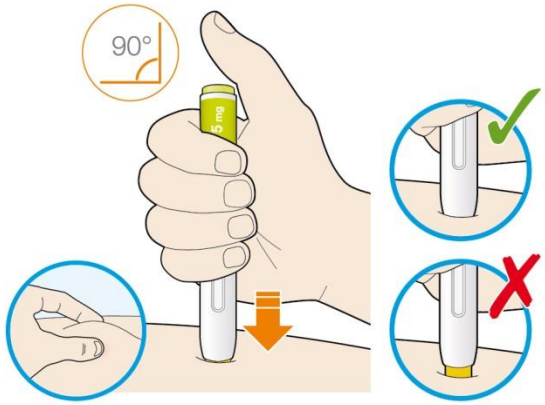


②Hold the Praluent pen like this.

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

③Press 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.



④ Push and immediately release the green button with your thumb.

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

⑤ Keep holding the pen against your skin after releasing the button

- The injection may take up to 20 seconds.

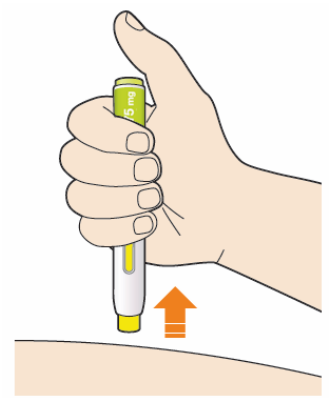
⑥ Check if the window has turned yellow, before removing the pen.

- 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 the local representative of the Marketing Authorization Holder for help. Do not give yourself a second dose without speaking to your doctor, pharmacist or nurse.

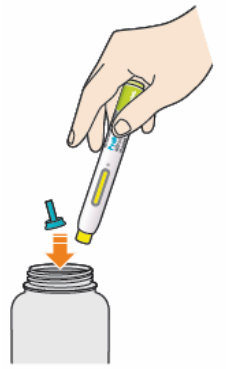
⑦ Pull pen away from your skin.

- Do not rub the skin after the injection.
- If you see any blood, press a cotton ball or gauze on the site until the bleeding stops.



⑧Throw away pen and cap

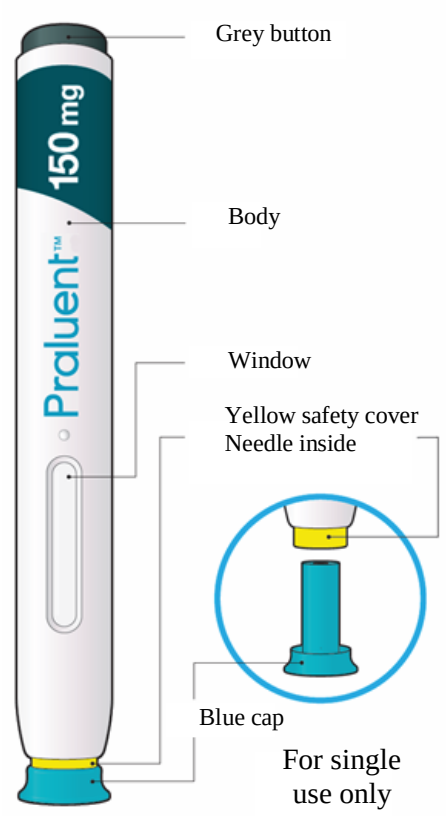
- Do not put the blue cap back on.
- Throw away pen and cap into a puncture-resistant container immediately after use.
- Ask your doctor, pharmacist or nurse how to throw away the container.
- Always keep the container out of the sight and reach of children.



Praluent pre-filled pen

Instructions for use

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



Important information

- The medicine is injected under your skin and can be given by yourself or someone else (caregiver).
- This pen can only be used for one single injection, and must be thrown away after use.

Do

✓ Keep the Praluent pen out of the sight and reach of children.
✓ Read all of the instructions carefully before using the Praluent pen.
✓ Follow these instructions every time you use a Praluent pen.

Do not

× 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.
× Do not shake the pen.
× Do not freeze the pen.
× Do not expose the pen to direct sunlight.

Keep this leaflet. If you have questions, ask your doctor, pharmacist or nurse or call the local representative of the Marketing Authorization Holder on the package leaflet.

STEP A: Getting ready for an injection

Before you start you will need:

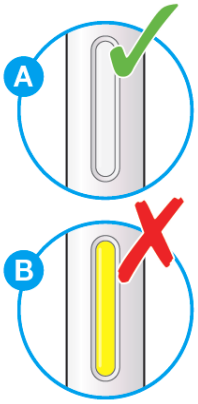
- the Praluent pen
- alcohol wipes
- cotton ball or gauze
- a puncture-resistant container (see Step B, 8).

① Look at the label on the pen.

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

② Look at the window.

- Check the liquid is clear, colourless to pale yellow and free from particles - if not, do not use (see picture A).
- You may see an air bubble. This is normal.
- Do not use if the window appears solid yellow (see picture B).



③ Let the pen warm up at room temperature for 30 to 40 minutes.

- Do not heat the pen, let it warm up on its own.
- Do not put the pen back in the refrigerator.

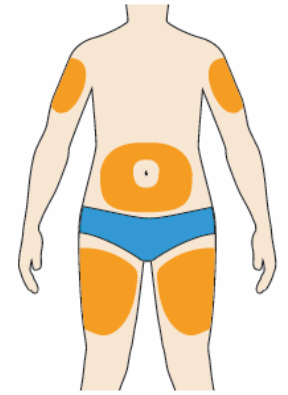
④ Prepare the injection site.

- Wash your hands with soap and water and dry with a towel.
- You can inject into your:
    - thigh

- belly (except for the 5 cm area around your navel)
- outer side of your upper arm

(See picture).

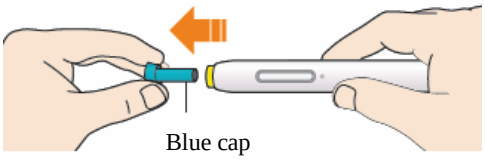
- You can stand or sit to give yourself an injection.
- Clean skin in the injection area with an alcohol wipe.
- Do not use skin that is tender, hard, red or hot.
- Do not use any area near a visible vein.
- Use a different spot each time you inject.
- Do not inject Praluent with other injectable medicines at the same spot.



STEP B: How to inject

① After completing all steps in "Step A: Getting ready for an injection", pull off the blue cap

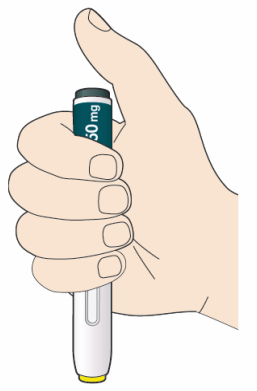
- Do not pull off the cap until you are ready to inject.
- Do not put the blue cap back on.



Blue cap

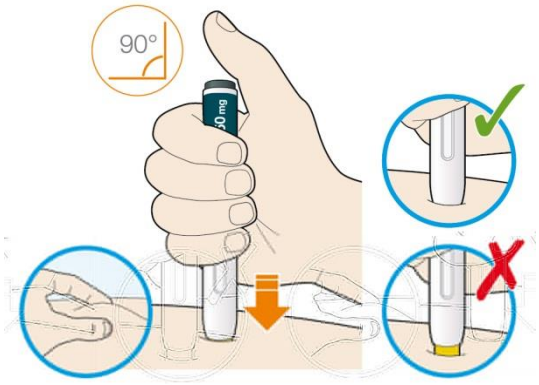
②Hold the Praluent pen like this.

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



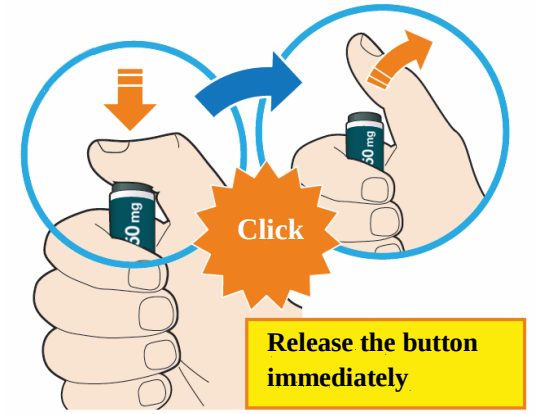
③Press the yellow safety cover on your skin at roughly a 90° angle.

- 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.



④ Push and immediately release the grey button with your thumb.

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



⑤ Keep holding the pen against your skin after releasing the button

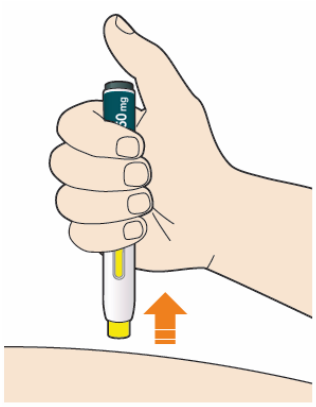
- The injection may take up to 20 seconds.

⑥ Check if 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 the local representative of the Marketing Authorization Holder for help. Do not give yourself a second dose without speaking to your doctor, pharmacist or nurse.

⑦ Pull pen away from your skin.

- Do not rub the skin after the injection.
- If you see any blood, press a cotton ball or gauze on the site until the bleeding stops.



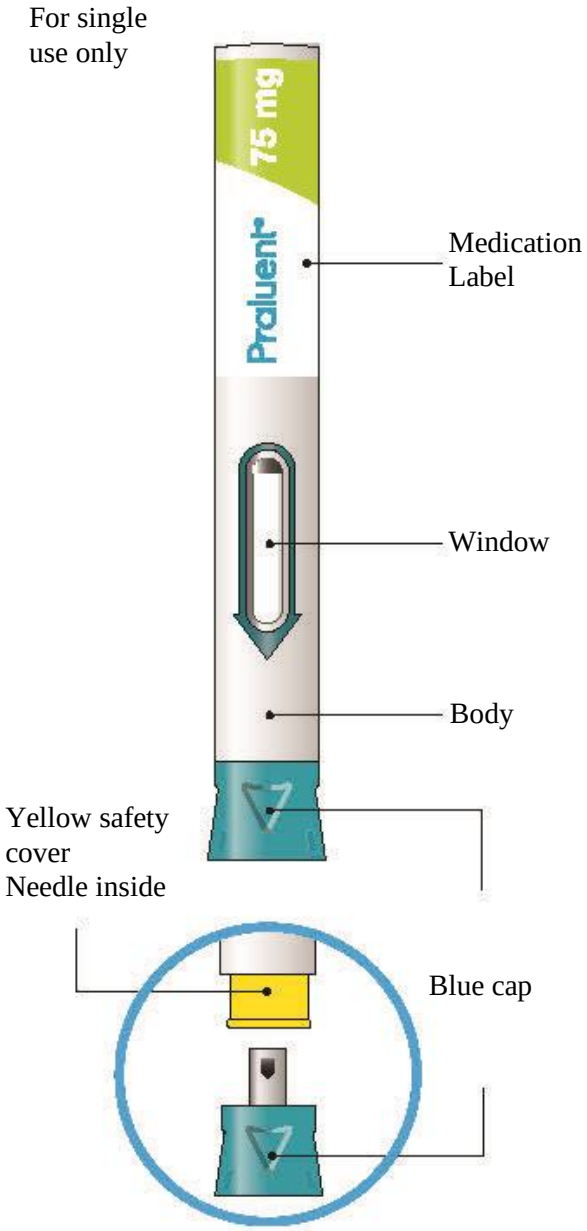
⑧Throw away pen and cap

- Do not put the blue cap back on.
- Throw away pen and cap into a puncture-resistant container immediately after use.
- Ask your doctor, pharmacist or nurse how to throw away the container.
- Always keep the container out of the sight and reach of children.

Praluent pre-filled pen

Instructions for use

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



Important information

- 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 one single injection, and must be thrown away after use.

Do

✓ Keep the Praluent pen out of the sight and reach of children.
✓ Read all of the instructions carefully before using the Praluent pen.

✓ Follow these instructions every time you use a Praluent pen.

Do not

× 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.
× Do not shake the pen.
× Do not freeze the pen.
× Do not expose the pen to extreme heat.
× Do not expose the pen to direct sunlight.

Keep this leaflet. If you have questions, ask your doctor, pharmacist or nurse or call the local representative of the Marketing Authorization Holder on the package leaflet.

STEP A: Getting ready for an injection

Before you start you will need:

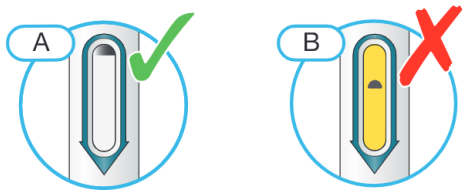
- the Praluent pen
- alcohol wipes
- cotton ball or gauze
- a puncture-resistant container (see Step B7).

① 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.
- Do not use the Praluent pen if it has been dropped on a hard surface or damaged.

② Look at the window.

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

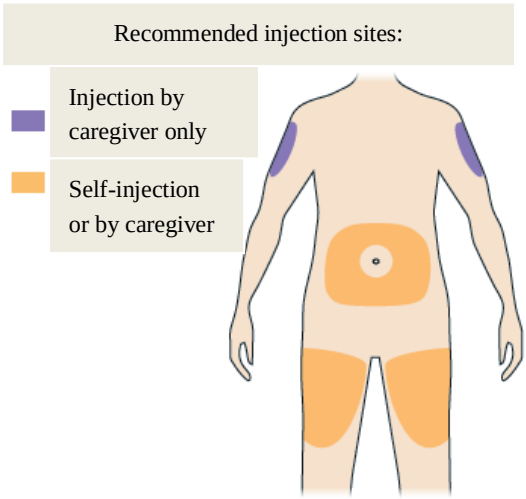


③ Let the pen warm up at room temperature for 30 to 40 minutes.

- This is important for administering the entire dose and helps minimize discomfort.
- Do not heat the pen, let it warm up on its own.
- Do not put the pen back in the refrigerator.

④ Prepare the injection site.

- Wash your hands with soap and water and dry with a towel.
- You can inject into (see PICTURE):
  - the top of your thighs
  - your belly (except for the 5 cm area around your navel)
  - outer side of your upper arm (to be given by your caregiver only)
- You can stand or sit to give yourself an injection.
- Clean skin in the injection area with an alcohol wipe.
- Do not use skin that is tender, hard, red or hot.
- Do not use any area near a visible vein.
- 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 Praluent with other injectable medicines at the same spot.

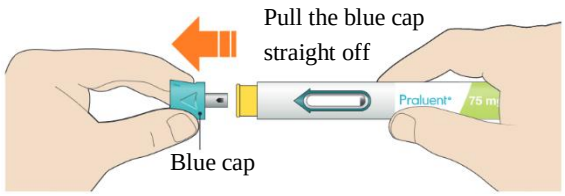


STEP B: How to inject

① After completing all steps in "Step A: Getting ready for an injection", pull off the blue cap

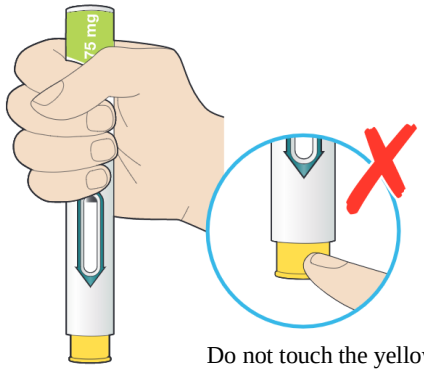
- Do not pull off the cap until you are ready to inject.
- Do not put the blue cap back on.

- Do not use the pen if the blue cap is missing or not securely attached.



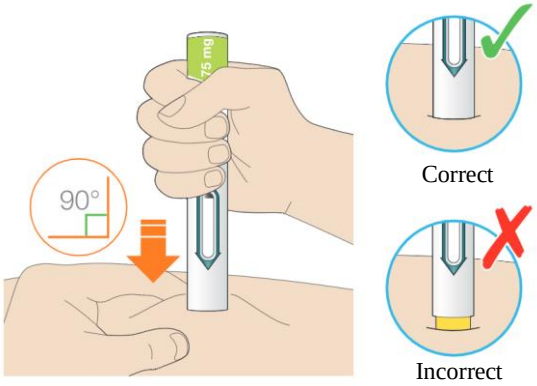
②Hold the Praluent pen like this.

- Do not touch the yellow safety cover. The needle is inside the yellow safety cover.
- Make sure you can see the window.
- Do not press the pen down against your skin until you are ready to inject.



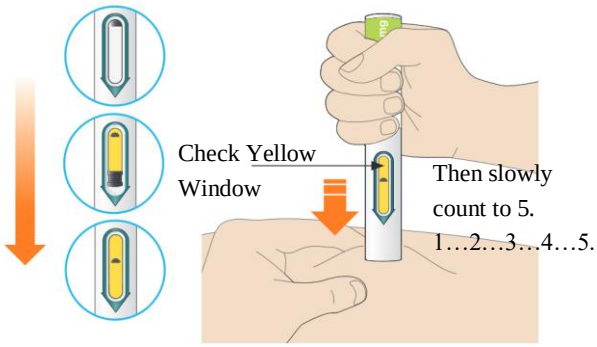
③Press the yellow safety cover on your skin at roughly a 90° angle.

- Pinch the skin to make sure the injection site is firm.
- Press the pen straight down against your skin until the yellow safety cover is pushed all the way into the pen and hold (see picture).
- The injection will not start until the yellow safety cover is fully depressed.
- There will be a click when the injection starts. The window will start to turn yellow.



④ Keep holding the pen against your skin

- You may hear a second click.
- Check that the entire window has turned yellow.
- Then, slowly count to 5.

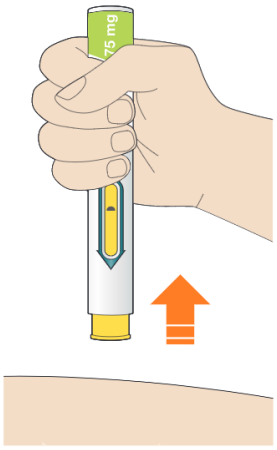


⑤ Check again that the window has turned yellow, before removing the pen.

- If the window has not turned completely yellow, remove the pen and call the local representative of the Marketing Authorization Holder for help.
- Do not give yourself a second injection without speaking to your doctor, pharmacist or nurse.

⑥ 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.



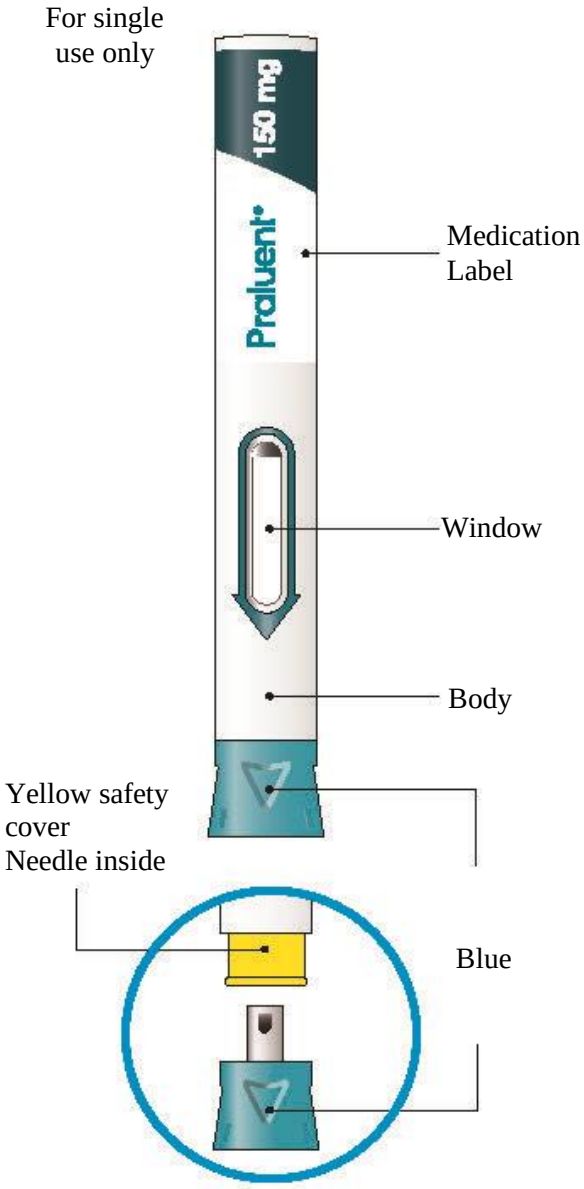
⑦Throw away pen and cap

- Do not put the blue cap back on.
- Throw away pen and cap into a puncture-resistant container immediately after use.
- Ask your doctor, pharmacist or nurse how to throw away the container.
- Always keep the container out of the sight and reach of children.

Praluent pre-filled pen

Instructions for use

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



Important information

- 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 one single injection and must be thrown away after use.

Do

✓ Keep the Praluent pen out of the sight and reach of children.
✓ Read all of the instructions carefully before using the Praluent pen.
✓ Follow these instructions every time you use a Praluent pen.

Do not

- × 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.
- × Do not shake the pen.
- × Do not freeze the pen.
- × Do not expose the pen to extreme heat.
- × Do not expose the pen to direct sunlight.

Keep this leaflet. If you have questions, ask your doctor, pharmacist or nurse or call the local representative of the Marketing Authorization Holder on the package leaflet.

STEP A: Getting ready for an injection

Before you start you will need:

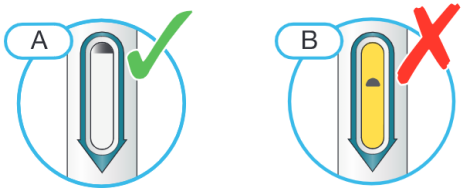
- the Praluent pen
- alcohol wipes
- cotton ball or gauze
- a puncture-resistant container (see Step B7).

① 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.
- Do not use the Praluent pen if it has been dropped on a hard surface or damaged.

② Look at the window.

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

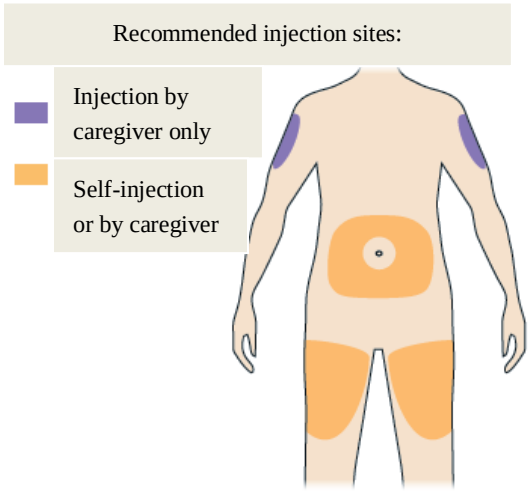


③ Let the pen warm up at room temperature for 30 to 40 minutes.

- This is important for administering the entire dose and helps minimize discomfort.
- Do not heat the pen, let it warm up on its own.
- Do not put the pen back in the refrigerator.

④ Prepare the injection site.

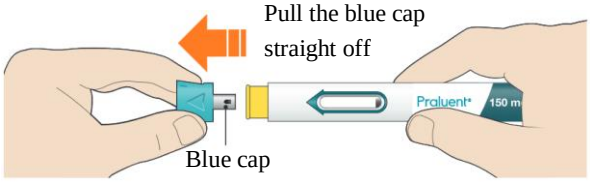
- Wash your hands with soap and water and dry with a towel.
- You can inject into (see PICTURE):
  - the top of your thighs
  - your belly (except for the 5 cm area around your navel)
  - outer side of your upper arm (to be given by your caregiver only)
- You can stand or sit to give yourself an injection.
- Clean skin in the injection area with an alcohol wipe.
- Do not use skin that is tender, hard, red or hot.
- Do not use any area near a visible vein.
- 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 Praluent with other injectable medicines at the same spot.



STEP B: How to inject

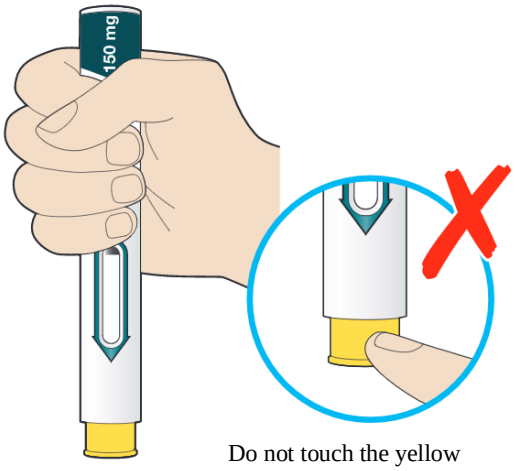
① After completing all steps in "Step A: Getting ready for an injection", pull off the blue cap

- Do not pull off the cap until you are ready to inject.
- Do not put the blue cap back on.
- Do not use the pen if the blue cap is missing or not securely attached.



②Hold the Praluent pen like this.

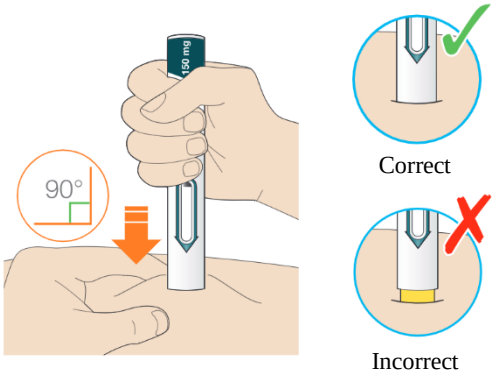
- Do not touch the yellow safety cover. The needle is inside the yellow safety cover.
- Make sure you can see the window.
- Do not press the pen down against your skin until you are ready to inject.



Do not touch the yellow safety cover

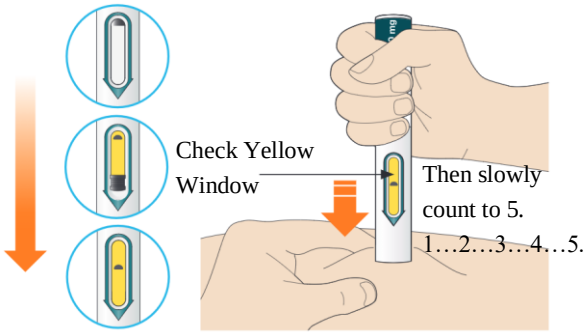
③Press the yellow safety cover on your skin at roughly a 90° angle.

- Pinch the skin to make sure the injection site is firm.
- Press the pen straight down against your skin until the yellow safety cover is pushed all the way into the pen and hold (see picture).
- The injection will not start until the yellow safety cover is fully depressed.
- There will be a click when the injection starts. The window will start to turn yellow.



④ Keep holding the pen against your skin

- You may hear a second click.
- Check that the entire window has turned yellow.
- Then, slowly count to 5.

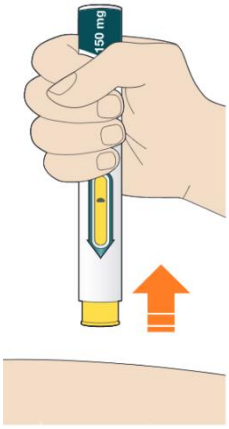


⑤ Check if the window has turned yellow, before removing the pen.

- If the window has not turned completely yellow, remove the pen and call the local representative of the Marketing Authorization Holder for help.
- Do not give yourself a second injection without speaking to your doctor, pharmacist or nurse.

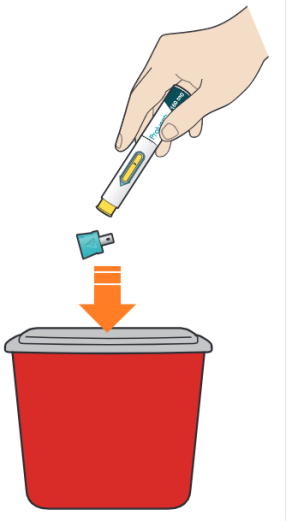
⑥ Pull pen away from your skin.

- 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.



⑦Throw away pen and cap

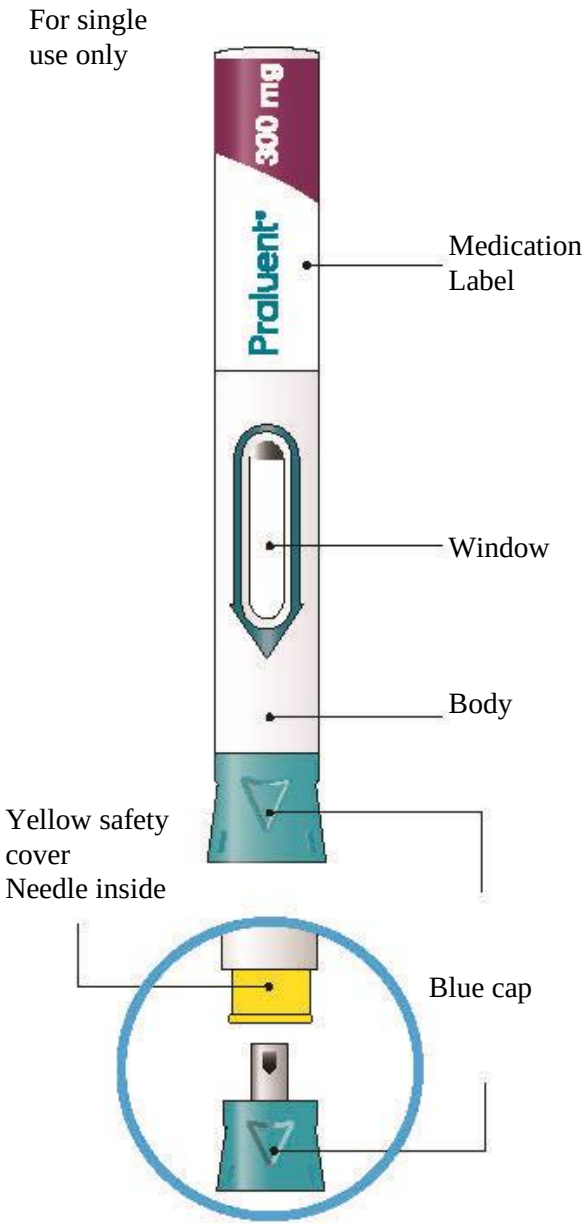
- Do not put the blue cap back on.
- Throw away pen and cap into a puncture-resistant container immediately after use.
- Ask your doctor, pharmacist or nurse how to throw away the container.
- Always keep the container out of the sight and reach of children.



Praluent pre-filled pen

Instructions for use

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



Important information

- 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 one single injection and must be thrown away after use.

Do

✓ Keep the Praluent pen out of the sight and reach of children.
✓ Read all of the instructions carefully before using the Praluent pen.

✓ Follow these instructions every time you use a Praluent pen.

Do not

× 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.
× Do not shake the pen.
× Do not freeze the pen.
× Do not expose the pen to extreme heat.
× Do not expose the pen to direct sunlight.

Keep this leaflet. If you have questions, ask your doctor, pharmacist or nurse or call the local representative of the Marketing Authorization Holder on the package leaflet.

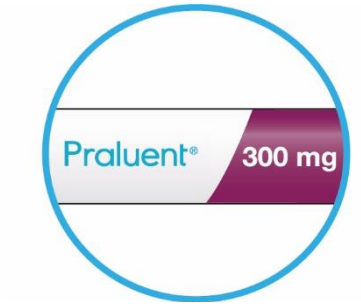
STEP A: Getting ready for an injection

Before you start you will need:

- the Praluent pen
- alcohol wipes
- cotton ball or gauze
- a puncture-resistant container (see Step B7).

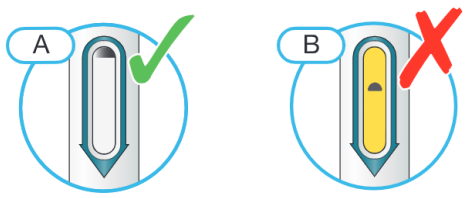
① Look at the label on the pen.

- Check that you have the correct product and the correct dose.
- Check the expiration date: do not use if this date has passed.
- Do not use the Praluent pen if it has been dropped on a hard surface or damaged.



② Look at the window.

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

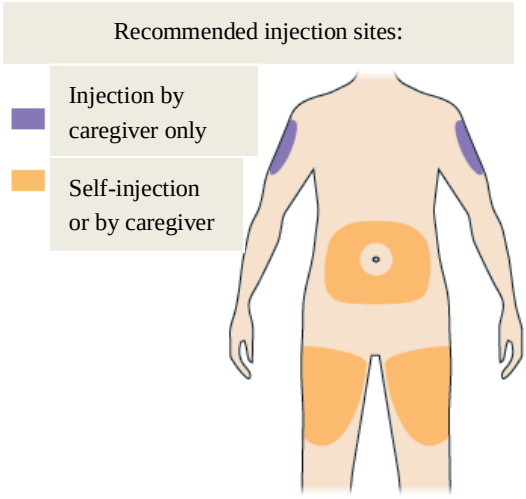


③ Let the pen warm up at room temperature for 45 minutes.

- This is important for administering the entire dose and helps minimize discomfort.
- Do not heat the pen, let it warm up on its own.
- Do not put the pen back in the refrigerator.

④ Prepare the injection site.

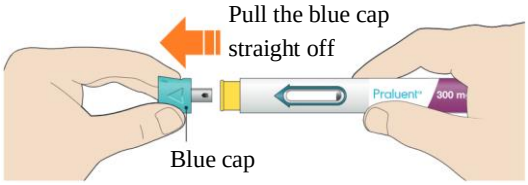
- Wash your hands with soap and water and dry with a towel.
- You can inject into (see PICTURE):
    - the top of your thighs
    - your belly (except for the 5 cm area around your navel)
    - outer side of your upper arm (to be given by your caregiver only)
- You can stand or sit to give yourself an injection.
- Clean skin in the injection area with an alcohol wipe.
- Do not use skin that is tender, hard, red or hot.
- Do not use any area near a visible vein.
- 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 Praluent with other injectable medicines at the same spot.



STEP B: How to inject

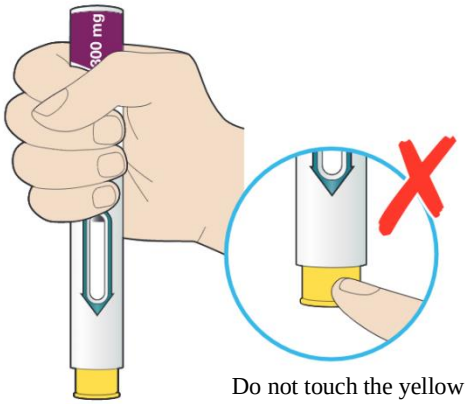
① After completing all steps in "Step A: Getting ready for an injection", pull off the blue cap

- Do not pull off the cap until you are ready to inject.
- Do not put the blue cap back on.
- Do not use the pen if the blue cap is missing or not securely attached.



②Hold the Praluent pen like this.

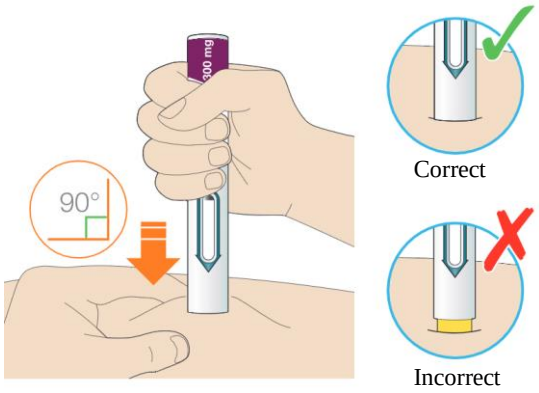
- Do not touch the yellow safety cover. The needle is inside the yellow safety cover.
- Make sure you can see the window.
- Do not press the pen down against your skin until you are ready to inject.



Do not touch the yellow safety cover

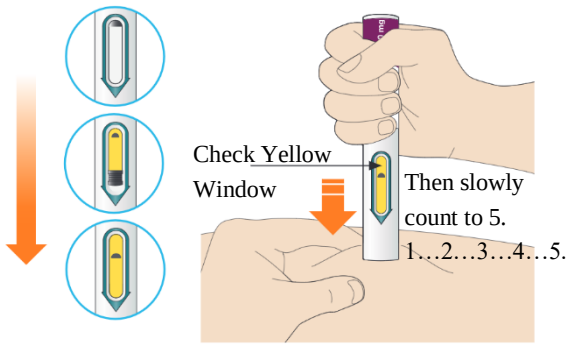
③Press the yellow safety cover on your skin at roughly a 90° angle.

- Pinch the skin to make sure the injection site is firm.
- Press the pen straight down against your skin until the yellow safety cover is pushed all the way into the pen and hold (see picture).
- The injection will not start until the yellow safety cover is fully depressed.
- There will be a click when the injection starts. The window will start to turn yellow.



④ Keep holding the pen against your skin

- You may hear a second click.
- Check that the entire window has turned yellow.
- Then, slowly count to 5.

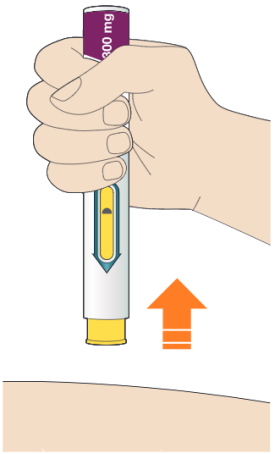


⑤ Check again that the window has turned yellow, before removing the pen.

- If the window has not turned completely yellow, remove the pen and call the local representative of the Marketing Authorization Holder for help.
- Do not give yourself a second injection without speaking to your doctor, pharmacist or nurse.

⑥ 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.



⑦Throw away pen and cap

- Do not put the blue cap back on.
- Throw away pen and cap into a puncture-resistant container immediately after use.
- Ask your doctor, pharmacist or nurse how to throw away the container.
- Always keep the container out of the sight and reach of children.

Package leaflet: Information for the user

Praluent 75 mg solution for injection in a pre-filled syringe
Praluent 150 mg solution for injection in a pre-filled syringe
alirocumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Praluent is and what it is used for

What Praluent is
- Praluent contains the active substance alirocumab.
- Praluent is a monoclonal antibody (a type of specialised protein designed to attach to a target substance in the body). Monoclonal antibodies are proteins that recognise and bind to other unique proteins. Alirocumab binds to PCSK9.

How Praluent works
Praluent helps lower your levels of "bad" cholesterol (also called "LDL cholesterol"). Praluent blocks a protein called PCSK9.
- PCSK9 is a protein secreted by liver cells.
- "Bad" cholesterol is normally removed from your blood by binding to specific "receptors" (docking stations) in your liver.
- PCSK9 lowers the number of these receptors in the liver – this causes your "bad" cholesterol to be higher than it should.
- By blocking PCSK9, Praluent increases the number of receptors available to help remove the "bad" cholesterol – this lowers your "bad" cholesterol levels.

What Praluent is used for
- Adults with high cholesterol levels in their blood (hypercholesterolaemia, heterozygous familial and non-familial, or mixed dyslipidaemia).
- Adults with high cholesterol levels in their blood and with cardiovascular disease to reduce cardiovascular risk.

It is given:
- together with a statin (a commonly used medicine that treats high cholesterol) or other cholesterol lowering medicines, if the maximum dose of a statin does not lower levels of cholesterol sufficiently or,
- alone or together with other cholesterol lowering medicines when statins are not tolerated or cannot be used.

Continue to follow your cholesterol-lowering diet while taking this medicine.

2. What you need to know before you use Praluent

Do not use Praluent
- if you are allergic to alirocumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Praluent.

If you develop a serious allergic reaction, stop using Praluent, talk to your doctor right away. Sometimes serious allergic reactions such as hypersensitivity, including angioedema (difficulties breathing, or swelling of the face, lips, throat or tongue), nummular eczema (reddish skin spots sometimes with blisters), and hypersensitivity vasculitis (which is a specific form of a hypersensitivity reaction with symptoms such as diarrhoea, with a rash, or purple-coloured skin spots on the skin) have occurred. For allergic reactions that may occur while taking Praluent, see section 4.

Tell your doctor if you have kidney or liver disease before using this medicine, because Praluent has been studied in few patients with severe kidney disease and not in patients with severe liver disease.

Children and adolescents
Praluent should not be given to children and adolescents under 18 years old because there is limited experience of using the medicine in these age groups.

Other medicines and Praluent
Tell your doctor, pharmacist or nurse if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.
Praluent is not recommended during pregnancy or breast-feeding.

Driving and using machines
This medicine is not expected to have any effect on your ability to drive or use machines.

3. How to use Praluent

Always use this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to inject
Your doctor will tell you which dose is right for you and how often to inject (75 mg or 150 mg once every 2 weeks, or 300 mg once every 4 weeks/monthly). Your doctor will check your cholesterol levels and may adjust the dose (up or down) during treatment.
Always check the label of your syringe to make sure you have the right medicine and the right strength.

When to inject
Inject Praluent once every 2 weeks (for the 75 mg or 150 mg dose), or once every 4 weeks/monthly (for the 300 mg dose). To give the 300 mg dose, two 150 mg injections should be given in a row at two different injection sites.

Before you inject
Praluent should be allowed to warm to room temperature prior to use.
Read the detailed instructions for use leaflet before you inject Praluent.

Where to inject
Praluent is injected under your skin into the thigh, abdomen or upper arm.

Read the detailed instructions for use leaflet on where to inject.

Learning how to use the pre-filled syringe
Before you use the syringe for the first time, your doctor, pharmacist or nurse will show you how to inject Praluent.

- Always read the **"Instructions for Use"** provided in the box.
- Always use the syringe as described in the **"Instructions for Use".**

If you use more Praluent than you should
If you use more Praluent than you should, talk to your doctor, pharmacist or nurse.

If you forget to use Praluent
If you miss a dose of Praluent, inject your missed dose as soon as you can. Then take your next dose at your regular scheduled time. This will keep you on the original schedule. If you are not sure when to inject Praluent, call your doctor, pharmacist or nurse.

If you stop using Praluent
Do not stop using Praluent without talking with your doctor. If you stop using Praluent, your cholesterol levels can increase.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you develop a serious allergic reaction, stop using Praluent , talk to your doctor right away. Sometimes serious allergic reactions such as hypersensitivity (difficulties breathing), nummular eczema (reddish skin spots sometimes with blisters), and hypersensitivity vasculitis (which is a specific form of a hypersensitivity reaction with symptoms such as diarrhoea, with a rash, or purple-coloured skin spots on the skin) have occurred (may affect up to 1 in 1,000 people).

Other side effects are:
Common (may affect up to 1 in 10 people)

- redness, itching, swelling, pain/tenderness where the medicine was injected (local injection site reactions)
- upper respiratory tract signs or symptoms such as sore throat, running nose, sneezing
- itching (pruritus).

Rare (may affect up to 1 in 1,000 people)

- red and itchy raised bumps or hives (urticaria)

Not Known

The following side effects have been reported since the marketing of Praluent, but how often they occur is not known:

- flu-like illness
- difficulties breathing, or swelling of the face, lips, throat or tongue (angioedema)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Praluent

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C). Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

If needed, individual pre-filled syringes may be kept outside the refrigerator below 25°C for a maximum of 30 days. Protect from light. After removal from the refrigerator, Praluent must be used within 30 days or discarded.

Do not use this medicine if it looks discoloured or cloudy, or if it contains visible flakes or particles.

After use put the syringe into a puncture-resistant container. Ask your doctor, pharmacist or nurse how to throw away the container. Do not recycle the container.

Do not throw away any medicines via wastewater or household waste.
Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Praluent contains

- The active substance is alirocumab.

  Praluent 75 mg solution for injection in pre-filled syringe
  Each single-use syringe contains 75 milligrams of alirocumab.

  Praluent 150 mg solution for injection in pre-filled syringe
  Each single-use syringe contains 150 milligrams of alirocumab.

- The other ingredients are histidine, sucrose, polysorbate 20 and water for injections.

What Praluent looks like and contents of the pack
Praluent is a clear, colourless to pale yellow solution for injection that comes in a pre-filled syringe.

Praluent 75 mg solution for injection in pre-filled syringe
Each pre-filled syringe with green plunger contains 1 ml of solution, delivering one single dose of 75 milligrams of alirocumab.
It is available in pack size of 1, 2 or 6 pre-filled syringes.

Praluent 150 mg solution for injection in pre-filled syringe
Each pre-filled syringe with grey plunger contains 1 ml of solution, delivering one single dose of 150 milligrams of alirocumab.
It is available in pack size of 1, 2 or 6 pre-filled syringes.

Not all presentations and pack sizes may be marketed.

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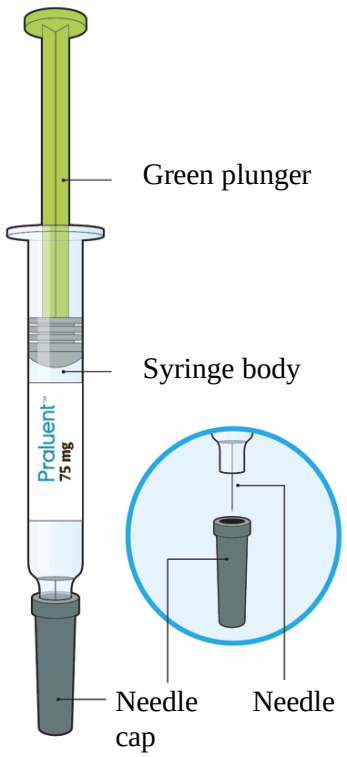
This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/

Praluent pre-filled syringe

Instructions for use

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



Important information

- The medicine is injected under your skin and can be given by yourself or someone else (caregiver).
- This syringe can only be used for one single injection, and must be thrown away after use.

Do

✓ Keep the Praluent syringe out of the sight and reach of children.
✓ Read all of the instructions carefully before using the Praluent syringe.
✓ Follow these instructions every time you use a Praluent syringe.

Do not

× Do not touch the needle.
× Do not use the syringe if it has been dropped or damaged.
× Do not use the syringe if the grey needle cap is missing or not securely attached.
× Do not re-use a syringe.
× Do not shake the syringe.
× Do not freeze the syringe.
× Do not expose syringe to direct sunlight.

Keep this leaflet. If you have questions, ask your doctor, pharmacist or nurse or call the local representative of the Marketing Authorization Holder on the package leaflet.

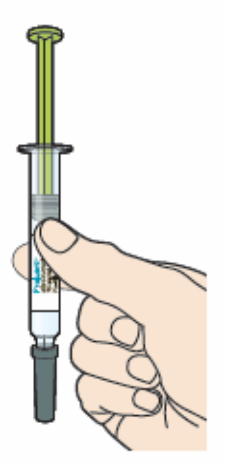
STEP A: Getting ready for an injection

Before you start you will need:

- the Praluent syringe
- alcohol wipes

- cotton ball or gauze
- a puncture-resistant container (see Step B, 6).

① Before you start.
- Take the syringe out of the packaging by holding the syringe body.

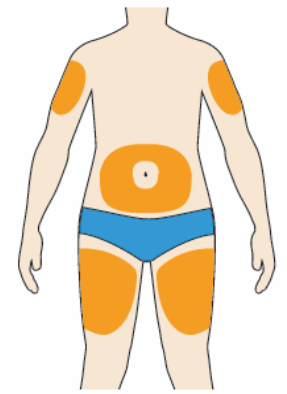


② Look at the label on the syringe.
- Check that you have the correct product and the correct dose (green plunger for 75 mg/ml).
- Check the use by date and do not use if this date has passed.
- Check the liquid is clear, colourless to pale yellow and free from particles; if not, do not use.
- Check that the syringe is not open or damaged.

③ Let the syringe warm up at room temperature for 30 to 40 minutes.
- Do not heat the syringe, let it warm up on its own.
- Do not put the syringe back in the refrigerator.

④ Prepare the injection site.
- Wash your hands with soap and water and dry with a towel.
- You can inject into your:
  - thigh
  - belly (except for the 5 cm area around your navel)
  - outer side of your upper arm

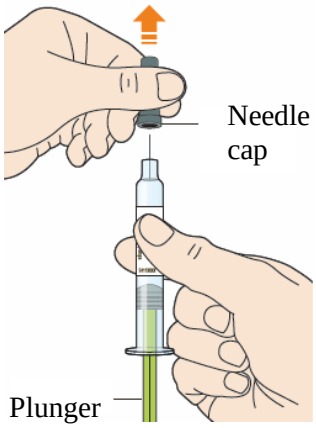
  (See picture).
- You can stand or sit to give yourself an injection.
- Clean skin in the injection area with an alcohol wipe.
- Do not use skin that is tender, hard, red or hot.
- Do not use any area near a visible vein.
- Use a different spot each time you inject.
- Do not inject Praluent with other injectable medicines at the same spot.



STEP B: How to inject

① After completing all steps in "Step A: Getting ready for an injection", pull off the needle cap.

- Do not pull off the cap until you are ready to inject.
- Hold the syringe in the middle of the syringe body with the needle pointing away from you.
- Keep your hand away from the plunger.
- You may see an air bubble. This is normal. Do not get rid of any air bubbles in the syringe before the injection.
- Do not put the grey cap back on.

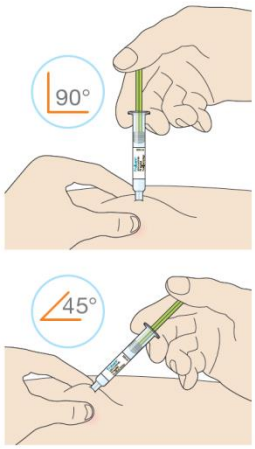


② If needed pinch the skin.

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

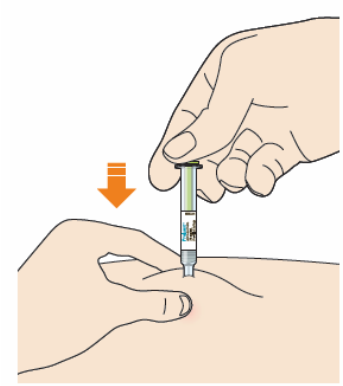
③ Insert the needle into the fold of skin with a quick dart-like motion.

- Use a 90º angle if you can pinch 5 cm of skin.
- Use a 45° angle if you can only pinch 2 cm of skin.



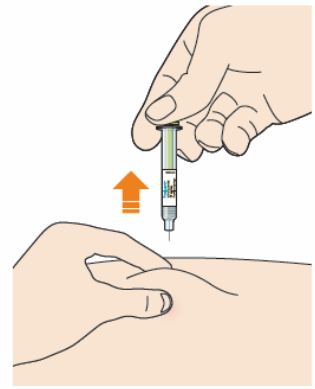
④ Push the plunger down.

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



⑤ Before you remove the needle check the syringe is empty.

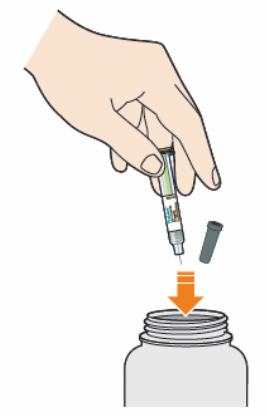
- Do not remove the syringe until it is completely empty.
- Pull the needle out of the skin at the same angle as it was inserted.
- Do not rub the skin after the injection.
- If you see any blood, press a cotton ball or gauze on the site until the bleeding stops.



⑥ Throw away syringe and cap

- Do not put the grey needle cap back on.
- Do not re-use the syringe.
- Throw away syringe and cap into a puncture-resistant container immediately after use.
- Ask your doctor, pharmacist or nurse how to throw away the container.

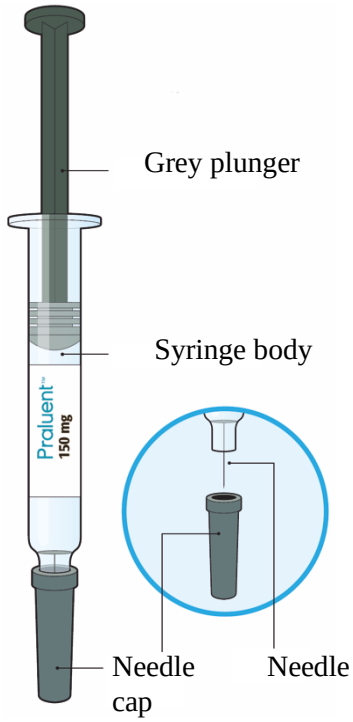
- Always keep the container out of the sight and reach of children.



Praluent pre-filled syringe

Instructions for use

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



Important information

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- This syringe can only be used for one single injection, and must be thrown away after use.

Do

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Keep this leaflet. If you have questions, ask your doctor, pharmacist or nurse or call the local representative of the Marketing Authorization Holder on the package leaflet.

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Before you start you will need:

- the Praluent syringe

- alcohol wipes
- cotton ball or gauze
- a puncture-resistant container (see Step B, 6).

① Before you start.

- Take the syringe out of the packaging by holding the syringe body.

② Look at the label on the syringe.

- Check that you have the correct product and the correct dose (grey plunger for 150 mg/ml).
- Check the use by date and do not use if this date has passed.
- Check the liquid is clear, colourless to pale yellow and free from particles; if not, do not use.
- Check that the syringe is not open or damaged.

③ Let the syringe warm up at room temperature for 30 to 40 minutes.

- Do not heat the syringe, let it warm up on its own.
- Do not put the syringe back in the refrigerator.

④ Prepare the injection site.

- Wash your hands with soap and water and dry with a towel.
- You can inject into your:
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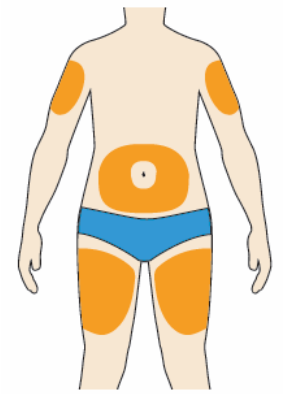

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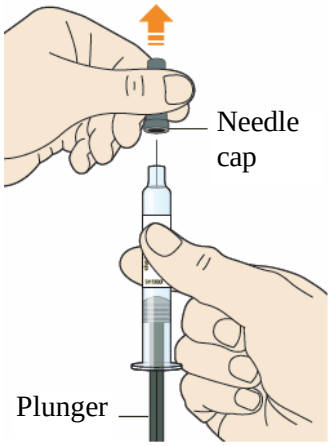

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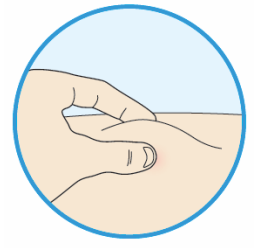

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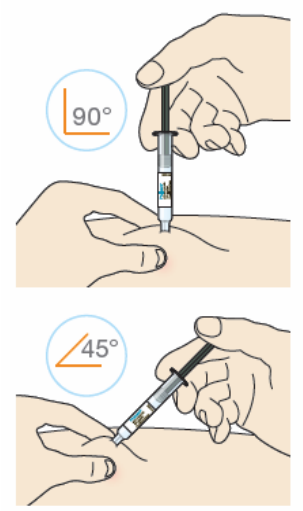
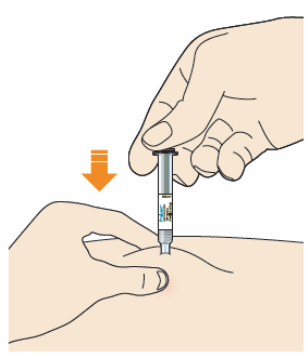


④ Push the plunger down.

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



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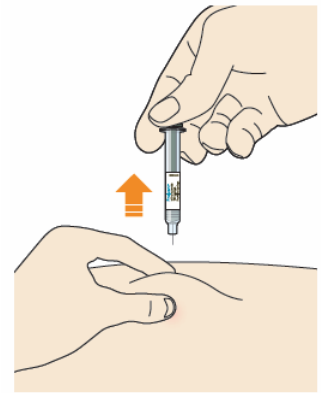

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