ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

150 mg/ml solution for injection:
Each single-use pre-filled pen contains 150 mg alirocumab in 1 ml solution.
Each single-use pre-filled syringe contains 150 mg alirocumab in 1 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

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

4.2 Posology and method of administration

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

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

The dose of Praluent can be individualised based on patient characteristics such as baseline LDL-C level, goal of therapy, and response. Lipid levels can be assessed 4 weeks after treatment initiation or titration, when steady-state LDL-C is usually achieved, and dose adjusted accordingly (up-titration or down-titration). Patients should be treated with the lowest dose necessary to achieve the desired LDL-C reduction.

If a dose is missed, the patient should administer the injection as soon as possible and thereafter resume treatment two weeks from the day of the missed dose.

Special populations

Paediatric population

The safety and efficacy of Praluent in children and adolescents less than 18 years of age have not been established. No data are available.

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.

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.

Method of administration

Subcutaneous use.

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

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

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

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

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

Precautions to be taken before handling

Praluent should be allowed to warm to room temperature prior to use. Praluent should be used as soon as possible after it has warmed up. (see section 6.6)

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

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

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 (see section 4.8). If signs or symptoms of serious allergic reactions occur, treatment with Praluent 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). Praluent 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). Praluent 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-fetal 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
Most common adverse reactions were local injection site reactions, upper respiratory tract signs and symptoms, and pruritus. Most common adverse reactions leading to treatment discontinuation in patients treated with Praluent were local injection site reactions.

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
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 following adverse reactions were reported in patients treated with alirocumab in pooled controlled studies:

Table 1 – Adverse Reactions reported in patients treated with alirocumab in pooled controlled studies

System organ class	***Common***	***Rare***
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
General disorders and administration site conditions	Injection site reactions**	

* 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).

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)

Special populations

Elderly

Although no safety issues were observed in patients over 75 years of age, data are limited in this age group. In controlled studies, 1158 patients (34.7%) treated with Praluent were ≥65 years of age and 241 patients (7.2%) treated with Praluent were ≥75 years of age. There were no significant differences observed in safety and efficacy with increasing age.

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

In pooled controlled studies, 796 of 3340 patients (23.8%) treated with Praluent had two consecutive values of LDL-C <25 mg/dL (<0.65 mmol/L), including 288 patients (8.6%) with two consecutive values <15 mg/dL (<0.39 mmol/L). These mostly occurred when patients were initiated and maintained on 150 mg Q2W of Praluent regardless of the baseline LDL-C value or the response to treatment. No adverse reaction was identified related to these LDL-C values.

Immunogenicity/ Anti-drug-antibodies (ADA)

In phase 3 studies, 4.8% of alirocumab-treated patients had a treatment-emergent ADA response as compared to 0.6% in the control group (placebo or ezetimibe). The majority of those patients exhibited transient low-titer ADA responses with no neutralising activity. Compared to patients who were ADA negative, patients with an ADA positive status did not exhibit any difference in alirocumab exposure, efficacy, or safety, except for a higher rate of injection site reactions. Only 1.2% of patients exhibited neutralising antibodies (NAb), all of them in the alirocumab group. Most of these patients had only one positive neutralising sample. Only 10 patients (0.3%) had two or more NAb positive samples. The data do not suggest a correlation between the presence of NAb and LDL-C lowering efficacy or safety. Immunogenicity data are highly dependent on the sensitivity and specificity of the ADA assay.

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

In controlled clinical studies, no safety issues were identified with more frequent dosing than the recommended every 2 week dosing schedule. There is no specific treatment for Praluent 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: not yet assigned ATC code: not yet assigned

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

Summary of the Phase 3 Clinical Trials Program

The efficacy of alirocumab was investigated in ten phase 3 trials (five placebo-controlled and five ezetimibe-controlled studies), involving 5296 randomised patients with hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, with 3188 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 2416 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 4 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 78 weeks in the LONG TERM study). 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
A cardiovascular outcomes trial whose primary endpoint is adjudicated major adverse cardiovascular events (MACE, i.e. CHD death, myocardial infarction, ischemic stroke, and unstable angina requiring hospitalisation) is ongoing.

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). MACE confirmed by adjudication were reported in 52 of 3182 (1.6%) patients in the alirocumab group and 33 of 1792 (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 1550 (4.6%) patients in the alirocumab group and in 40 of 788 (5.1%) patients in the placebo group; MACE confirmed by adjudication were reported in 27 of 1550 (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, 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 3182 patients) in the alirocumab group and 0.9% (17 of 1792 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 2310 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 2. 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 multicenter, 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

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/mL); [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)

Paediatric population
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. Steady state was reached after 2 to 3 doses with an accumulation ratio 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 (AUC_{0-14d}) 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.

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 evaluations 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 fetal 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

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C). Do not freeze.
Time out of refrigeration should not exceed a maximum of 24 hours at temperatures below 25°C.
Keep the pen or syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container

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

Pre-filled pen 75 mg:
The syringe components are assembled into a single-use pre-filled pen with a blue cap and a light green activation button.
Pre-filled pen 150 mg:
The syringe components are assembled into a single-use pre-filled pen with a blue cap and a dark grey activation button.

Pre-filled syringe 75 mg:
The syringe is equipped with a light green polypropylene plunger rod.
Pre-filled syringe 150 mg:
The syringe is equipped with a dark grey polypropylene plunger rod.

Pack size:
1, 2, or 6 pre-filled pens.
1, 2, or 6 pre-filled syringes.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution should be clear, colourless to pale yellow. If the solution is discoloured or contains visible particulate matter, the solution should not be used.

After use, place the pre-filled pen/ pre-filled syringe into a puncture resistant container and discard as required by local regulations. Do not recycle the container. Always keep the container out of the sight and reach of children. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
sanofi-aventis groupe
54, rue La Boétie
F – 75008 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1031/001
EU/1/15/1031/002
EU/1/15/1031/003
EU/1/15/1031/004
EU/1/15/1031/005
EU/1/15/1031/006
EU/1/15/1031/007
EU/1/15/1031/008
EU/1/15/1031/009
EU/1/15/1031/010
EU/1/15/1031/011
EU/1/15/1031/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

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 manufacturer of the biological active substance

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

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

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**

The requirements for submission of periodic safety update reports 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 shall submit the first periodic safety update report 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 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 (75 mg/ml).

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 and the detailed instructions for use 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.
Time out of refrigeration should not exceed a maximum of 24 hours at temperatures below 25°C.
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-aventis groupe
54, rue La Boétie
75008 Paris
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

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL – 75 mg

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

75 mg/ml
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 (150 mg/ml).

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 and the detailed instructions for use 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.
Time out of refrigeration should not exceed a maximum of 24 hours at temperatures below 25°C.
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-aventis groupe
54, rue La Boétie
75008 Paris
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

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL – 150 mg

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

150 mg/ml
1 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 (75 mg/ml).

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

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 and the detailed instructions for use 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.
Time out of refrigeration should not exceed a maximum of 24 hours at temperatures below 25°C.
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-aventis groupe
54, rue La Boétie
75008 Paris
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

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-aventis groupe

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 (150 mg/ml).

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 and the detailed instructions for use 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.
Time out of refrigeration should not exceed a maximum of 24 hours at temperatures below 25°C.
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-aventis groupe
54, rue La Boétie
75008 Paris
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

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-aventis groupe

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

alirocumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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). 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 about all your medical conditions, including allergies, 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 (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 in clinical studies. 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 is not recommended for children and adolescents under 18 years old. This is because there is no 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
Praluent is not recommended during pregnancy or 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.

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 (75 mg or 150 mg). 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.

Before you inject
Read the detailed instructions for use leaflet before you inject Praluent.

Where to inject
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 two weeks from the day you missed your dose. For example, if you normally inject every other Tuesday, keep injecting every other Tuesday. 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)

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.
Do not keep Praluent out of the refrigerator for more than 24 hours at temperatures below 25°C (do not store above 25°C).
Keep the pen in the outer carton in order to protect from light.

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. Always keep the container out of the sight and reach of children. 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. Each single-use pen contains either 75 milligrams (75 milligrams per ml) or 150 milligrams (150 milligrams per ml) of alirocumab.
- The other ingredients are histidine, sucrose, polysorbate 20 and water for injection.

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.

Each pre-filled pen with green 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.

Each pre-filled pen with grey 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.

Not all 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.

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

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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). 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 about all your medical conditions, including allergies, 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 (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 in clinical studies. 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 is not recommended for children and adolescents under 18 years old. This is because there is no 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
Praluent is not recommended during pregnancy or 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.

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 (75 mg or 150 mg). 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.

Before you inject
Read the detailed instructions for use leaflet before you inject Praluent.

Where to inject
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 two weeks from the day you missed your dose. For example, if you normally inject every other Tuesday, keep injecting every other Tuesday. 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)

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.
Do not keep Praluent out of the refrigerator for more than 24 hours at temperatures below 25°C (do not store above 25°C).
Keep the syringe in the outer carton in order to protect from light.

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. Always keep the container out of the sight and reach of children. 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. Each single-use syringe contains either 75 milligrams (75 milligrams per ml) or 150 milligrams (150 milligrams per ml) of alirocumab.
- The other ingredients are histidine, sucrose, polysorbate 20 and water for injection.

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.

Each pre-filled syringe with green plunger 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 syringes.

Each pre-filled syringe with grey plunger 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 syringes.

Not all pack sizes may be marketed.

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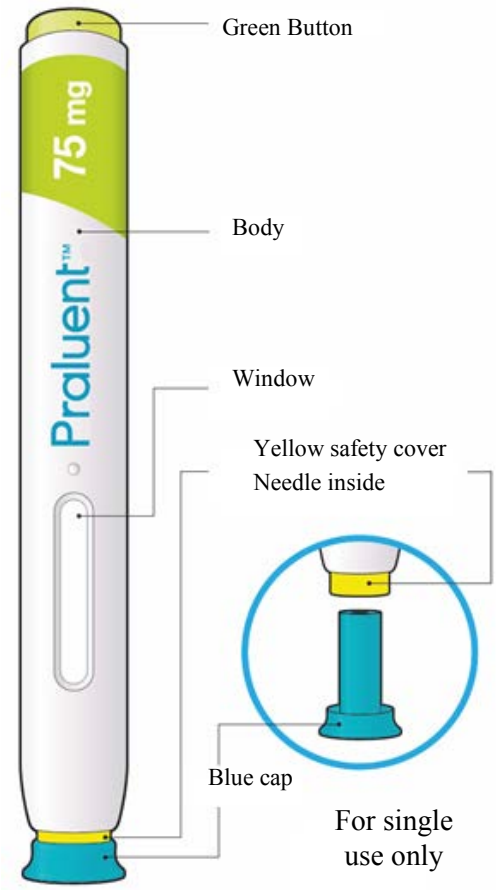
This leaflet was last revised in

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

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

Instructions for use

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



Important information

- The device is a single use pre-filled pen. It contains 75 mg of Praluent (alirocumab) in 1 ml.
- 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.
✓ Store unused pens in the refrigerator at 2°C to 8°C. For detailed storage conditions see separate package leaflet for Praluent.

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.

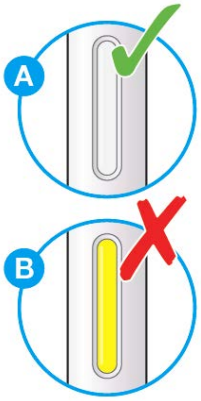
Keep this leaflet. If you have questions, ask your doctor, pharmacist or nurse or call the sanofi-aventis number on the package leaflet.

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).

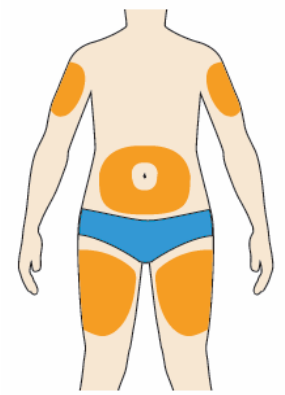


③ Let the pen warm up at room temperature for 30 to 40 minutes.
- Do not heat the pen, let it warm up on its own.
- Use the pen as soon as possible after it has warmed up.
- Do not put the pen back in the refrigerator.

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

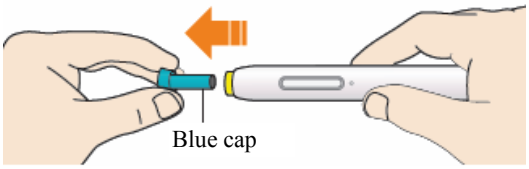
  (See picture).
- You can stand or sit to give yourself an injection.
- Clean skin in the injection area with an alcohol wipe.
- Do not use skin that is tender, hard, red or hot.
- Do not use any area near a visible vein.
- Use a different spot each time you inject.
- Do not inject Praluent with other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

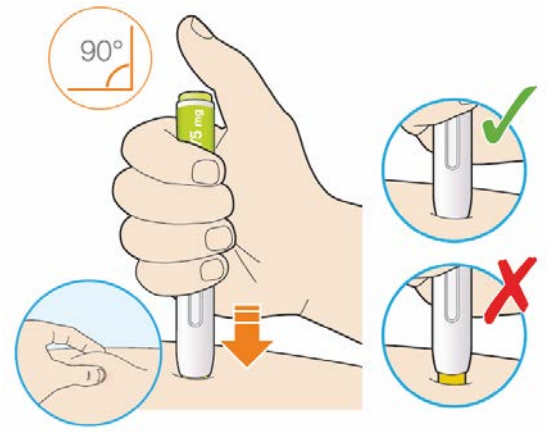


②Hold the Praluent pen like this.

- 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.

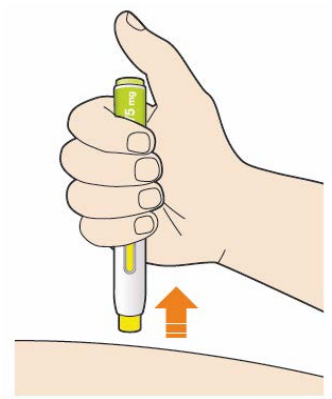
⑥ Check if the window has turned yellow, before removing the pen.

- 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 sanofi-aventis 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.



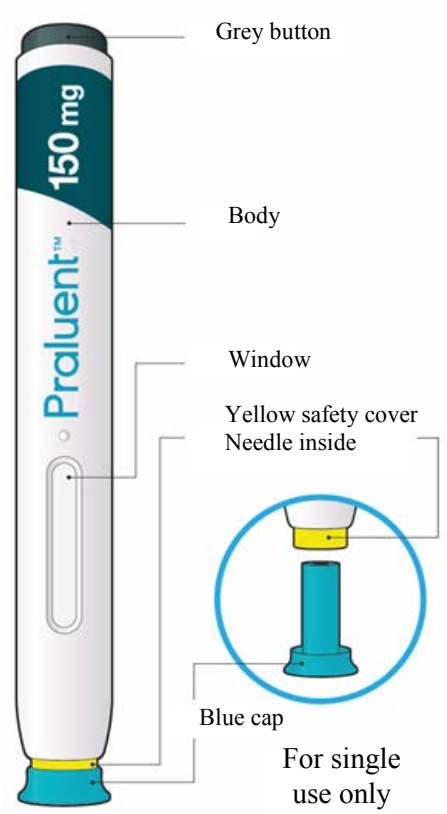
⑧Throw away pen and cap

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

Instructions for use

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



Important information

- The device is a single use pre-filled pen. It contains 150 mg of Praluent (alirocumab) in 1 ml.
- 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.
✓ Store unused pens in the refrigerator at 2°C to 8°C. For detailed storage conditions see separate package leaflet for Praluent.

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.

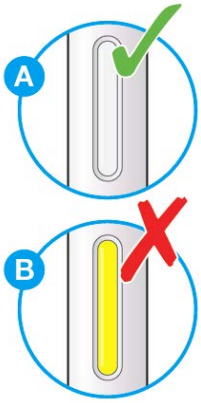
Keep this leaflet. If you have questions, ask your doctor, pharmacist or nurse or call the sanofi-aventis number on the package leaflet.

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).



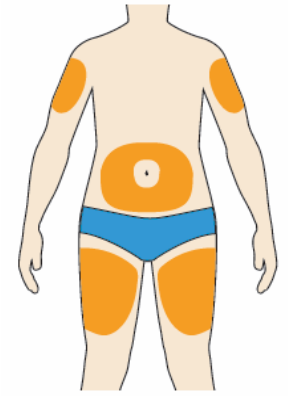
③ Let the pen warm up at room temperature for 30 to 40 minutes.
- Do not heat the pen, let it warm up on its own.
- Use the pen as soon as possible after it has warmed up.
- Do not put the pen back in the refrigerator.

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).

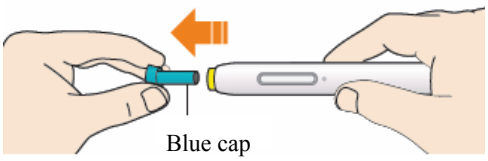
- You can stand or sit to give yourself an injection.
- Clean skin in the injection area with an alcohol wipe.
- Do not use skin that is tender, hard, red or hot.
- Do not use any area near a visible vein.
- Use a different spot each time you inject.
- Do not inject Praluent with other injectable medicines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

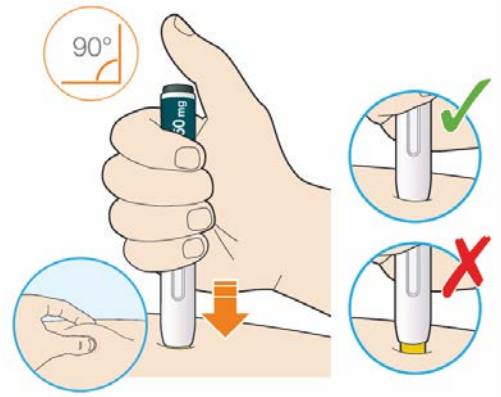


②Hold the Praluent pen like this.

- 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.

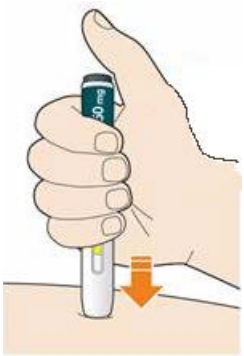


④ Push and immediately release the grey button with your thumb.

- 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.

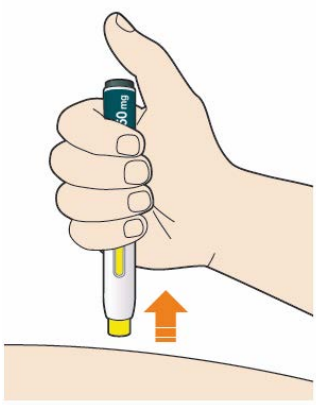


⑥ Check if the window has turned yellow, before removing the pen.

- 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 sanofi-aventis 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.



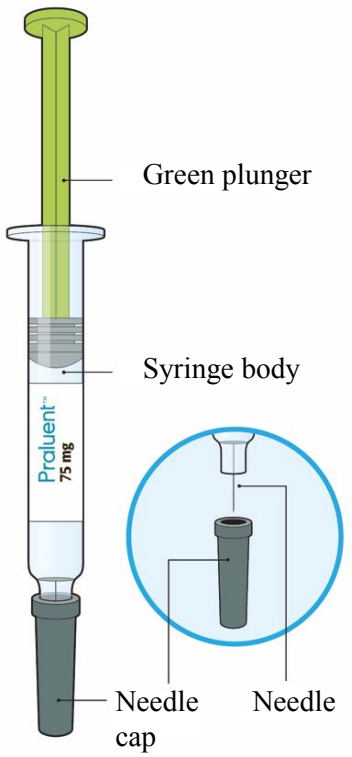
⑧Throw away pen and cap

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

Instructions for use

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



Important information

- The device is a single use pre-filled syringe. It contains 75 mg of Praluent (alirocumab) in 1 ml.
- 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.
✓ Store unused syringes in the refrigerator at 2°C to 8°C. For detailed storage conditions see separate package leaflet for Praluent.

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 sanofi-aventis number 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).

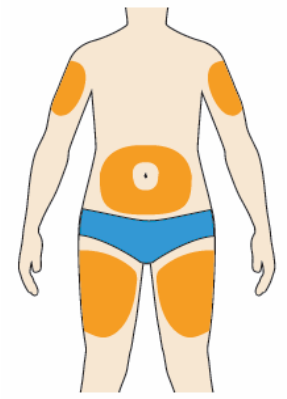
① Before you start.
- Take the syringe out of the packaging by holding the syringe body.

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.
- Use the syringe as soon as possible after it has warmed up.
- 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

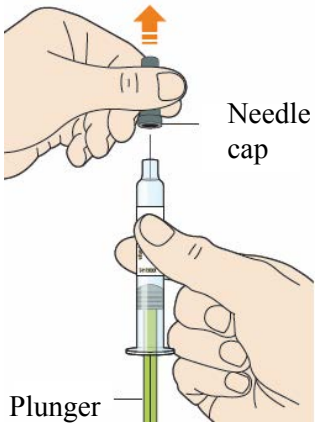
  (See picture).
- You can stand or sit to give yourself an injection.
- Clean skin in the injection area with an alcohol wipe.
- Do not use skin that is tender, hard, red or hot.
- Do not use any area near a visible vein.
- Use a different spot each time you inject.
- Do not inject Praluent with other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



STEP B: How to inject

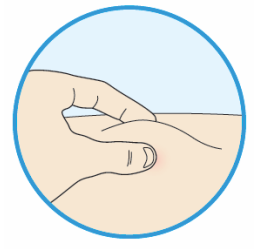
① After completing all steps in "Step A: Getting ready for an injection", pull off the needle cap.

- 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.



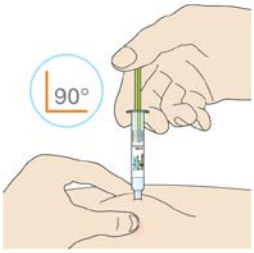
② If needed pinch the skin.

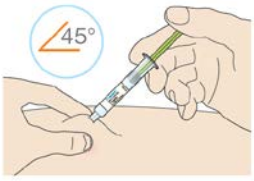
- Use your thumb and first finger to pinch a fold of skin at the injection site.
- Hold the skin like this for the whole injection.



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

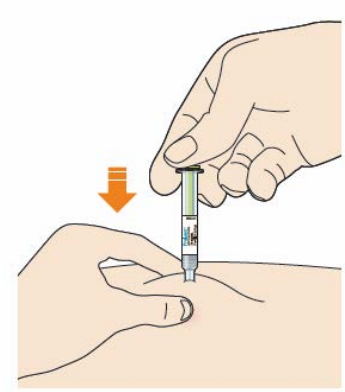
- Use a 90º angle if you can pinch 5 cm of skin.
- Use a 45° angle if you can only pinch 2 cm of skin.





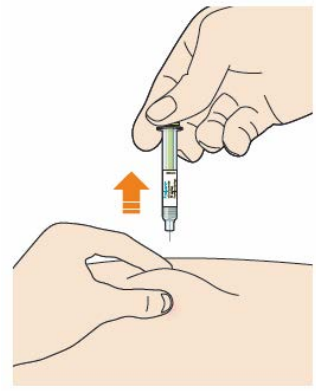
④ Push the plunger down.

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



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

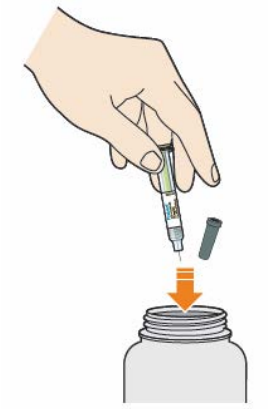
- Do not remove the syringe until it is completely empty.
- Pull the needle out of the skin at the same angle as it was inserted.
- Do not rub the skin after the injection.
- If you see any blood, press a cotton ball or gauze on the site until the bleeding stops.



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.

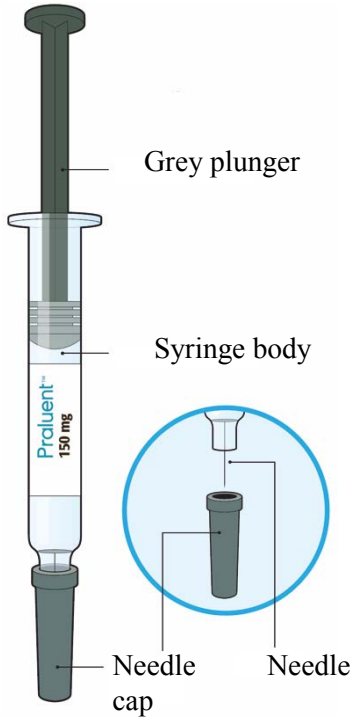
- Always keep the container out of the sight and reach of children.



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

Instructions for use

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



Important information

- The device is a single use pre-filled syringe. It contains 150 mg of Praluent (alirocumab) in 1 ml.
- 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.
✓ Store unused syringes in the refrigerator at 2°C to 8°C. For detailed storage conditions see separate package leaflet for Praluent.

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 sanofi-aventis number 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).

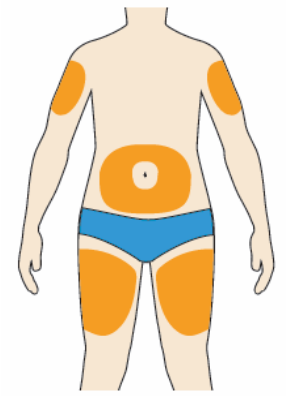
① Before you start.
- Take the syringe out of the packaging by holding the syringe body.

② Look at the label on the syringe.
- Check that you have the correct product and the correct dose (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.
- Use the syringe as soon as possible after it has warmed up.
- 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

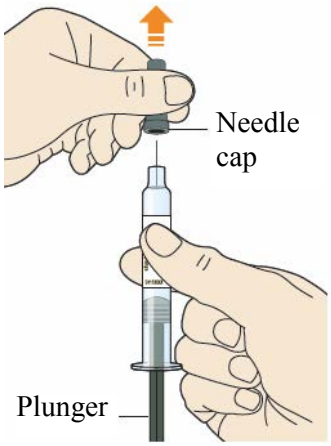
  (See picture).
- You can stand or sit to give yourself an injection.
- Clean skin in the injection area with an alcohol wipe.
- Do not use skin that is tender, hard, red or hot.
- Do not use any area near a visible vein.
- Use a different spot each time you inject.
- Do not inject Praluent with other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



STEP B: How to inject

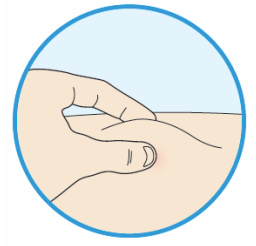
① After completing all steps in "Step A: Getting ready for an injection", pull off the needle cap.

- 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.

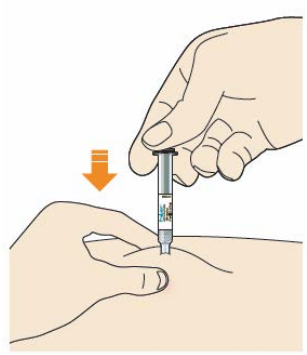


③ Insert the needle into the fold of skin with a quick dart-like motion.

- 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.

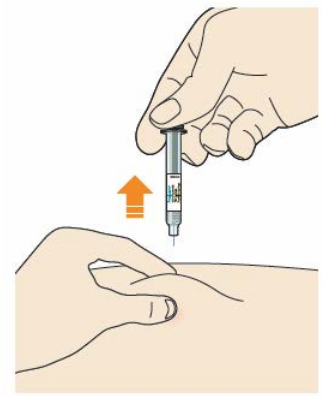
④ Push the plunger down.

- 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.