יוני 2024

PRALUENT 150 MG/ML (300 mg/ 2ml)

Solution for Injection in Prefilled Pen

חומר פעיל:

Praluent 150 mg/ml - Alirocumab 150mg / 1mL; Alirocumab 300mg / 2mL

רופא/ה ורוקח/ת נכבד/ה,

חברת סאנופי ישראל בע"מ שמחה לבשר על תחילת שיווק של פרזנטציה חדשה של התכשיר שבנדון: <u>עט מוכן להזרקה</u> **בנפח של 2 מ"ל**, המכיל **300 מ"ג Alirocumab** (כך שריכוז החומר הפעיל הינו 150 mg/ml).

<u>לתשומת לבכם:</u>

- התכשיר Praluent 150 mg/ml כבר משווק בפרזנטציית עט מוכן להזרקה בנפח של 1 מ"ל, בריכוז זהה של חומר פעיל (150 mg/ml) ומכיל 150 מ"ג Alirocumab.
- עט מוכן להזרקה בנפח 2 מ"ל הינו בעל הוראות מתן ושימוש שונות מעט מוכן להזרקה בנפח 1 מ"ל. העלון לרופא/לצרכן מפורסם במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס על ידי פניה לבעל הרישום.

התוויה מאושרת :

<u>Primary hypercholesterolaemia and mixed dyslipidaemia</u>

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

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

Established atherosclerotic cardiovascular disease

Praluent is indicated in adults with established atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:
- in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

- יצרן התכשיר הינו Sanofi Winthrop Industrie
- התכשיר נכלל בסל הבריאות
- התכשיר מופץ ע"י חברת נובולוג.

לקבלת מידע נוסף ניתן לפנות לבעל הרישום - סאנופי ישראל בע"מ, מתחם גרינוורק, ת.ד. 47 יקום, או בטלפון: 09-8633700.

בברכה,

חברת סאנופי ישראל בע"מ

1. NAME OF THE MEDICINAL PRODUCT

Praluent 75 mg/ml
Praluent 150 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml single-use pre-filled pen/syringe contains 75 mg or 150 mg alirocumab*.
Each 2 ml single-use pre-filled pen contains 300 mg alirocumab*.
*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.
Clear, colorless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary hypercholesterolaemia and mixed dyslipidaemia

Praluent is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:
- in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Established atherosclerotic cardiovascular disease

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

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

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

4.2 Posology and method of administration

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

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

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

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

Special populations
Elderly
No dose adjustment is needed for elderly patients

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

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

Body weight
No dose adjustment is needed in patients based on weight.

Paediatric population
Praluent is not indicated for children and adolescents under 18 years old.
The safety and efficacy of Praluent in children and adolescents less than 18 years of age have not been established.

Method of administration

Subcutaneous use.

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

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

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

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

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

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

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

Allergic reactions
General allergic reactions, including pruritus, as well as rare and sometimes serious allergic reactions such as hypersensitivity, nummular eczema, urticaria, and hypersensitivity vasculitis have been reported in clinical studies. Angioedema has been reported in the postmarketing setting (see section 4.8). If signs or symptoms of serious allergic reactions occur, treatment with alirocumab must be discontinued and appropriate symptomatic treatment initiated (see section 4.3).

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

Hepatic impairment

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

4.6 Fertility, pregnancy and lactation

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions, at recommended doses, are local injection site reactions (6.1%), upper respiratory tract signs and symptoms (2.0%), and pruritus (1.1%). Most common adverse reactions leading to treatment discontinuation in patients treated with alirocumab were local injection site reactions.

The safety profile in ODYSSEY OUTCOMES was consistent with the overall safety profile described in the phase 3 controlled trials.

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

Tabulated list of adverse reactions

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

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

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

Table 1 – Adverse reactions

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

* including mainly oropharyngeal pain, rhinorrhea, sneezing

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

Description of selected adverse reactions

Local injection site reactions

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

General allergic reactions

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

Special populations

Elderly

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

Every 4 week dosing study

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

discontinuation rate due to injection site reactions was 0.7% in the 300 mg once every 4 weeks treatment group and 0% in the placebo group.

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

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

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

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

Immunogenicity/Anti-drug-antibodies (ADA)

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
/https://sideeffects.health.gov.il

4.9 Overdose

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

5.PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

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

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

In a multicenter, double-blind, placebo-controlled, 14 week study, 13 patients with heterozygous familial hypercholesterolaemia (heFH) due to gain-of-function mutations in the PCSK9 gene were randomised to receive either alirocumab 150 mg Q2W or placebo. Mean baseline LDL-C was 151.5

mg/dL (3.90 mmol/L). At week 2, the mean reduction from baseline in LDL-C was 62.5% in the alirocumab-treated patients as compared to 8.8% in the placebo patients. At week 8, the mean reduction in LDL-C from baseline with all patients treated with alirocumab was 72.4%.

Pharmacodynamic effects

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

Clinical efficacy and safety in primary hypercholesterolaemia and mixed dyslipidaemia

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

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

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

The primary efficacy endpoint in all of the phase 3 studies was the mean percent reduction from baseline in LDL-C at week 24 as compared to placebo or ezetimibe. All of the studies met their primary endpoint. In general, administration of alirocumab also resulted in a statistically significant greater percent reduction in total cholesterol (Total-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (Apo B), and lipoprotein (a) [Lp(a)] as compared to placebo/ ezetimibe, whether or not patients were concomitantly being treated with a statin. Alirocumab also reduced triglycerides (TG), and increased high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-1 (Apo A-1) as compared to placebo. For detailed results see Table 2 below. Reduction in LDL-C was seen across age, gender, body mass index (BMI), race, baseline LDL-C levels, patients with heFH and non-heFH, patients with mixed dyslipidaemia, and diabetic patients. Although similar efficacy was observed in patients over 75 years, data are limited in this age group. LDL-C reduction was consistent regardless of concomitantly used statins and doses. A significantly higher proportion of patients achieved an LDL-C of <70 mg/dL (<1.81 mmol/L) in the alirocumab group as compared to placebo or ezetimibe at week 12 and week 24. In studies using the criteria-based up-titration regimen, a majority of patients achieved the pre-defined target LDL-C (based on their level of CV risk) on the 75 mg Q2W dose, and a majority of patients

maintained treatment on the 75 mg Q2W dose. The lipid-lowering effect of alirocumab was observed within 15 days after the first dose reaching maximum effect at approximately 4 weeks. With long-term treatment, efficacy was sustained over the duration of the studies (up to 2 years. Following discontinuation of alirocumab, no rebound in LDL-C was observed, and LDL-C levels gradually returned to baseline levels.

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

Evaluation of cardiovascular (CV) events

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

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

All-cause mortality

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

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

LONG TERM study

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

COMBO I study

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

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

FH I and FH II studies

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

HIGH FH study

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

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

COMBO II study

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

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

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

ALTERNATIVE study

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

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

MONO study

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

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

Mean Percent Change from Baseline in Placebo-Controlled Studies on Background Statin								
	LONG TERM (N=2310)		**FHI and FHII (N=732)**		**High FH (N=106)**		**COMBO I (N=311)**	
	Placebo	**Alirocumab**	**Placebo**	**Alirocumab**	**Placebo**	**Alirocumab**	**Placebo**	**Alirocumab**
Number of patients	780	1530	244	488	35	71	106	205
Mean Baseline LDL-C in mg/dL (mmol/L)	122.0 (3.16)	122.8 (3.18)	140.9 (3.65)	141.3 (3.66)	201.0 (5.21)	196.3 (5.10)	104.6 (2.71)	100.3 (2.60)
Week 12								
LDL-C (ITT)[a]	1.5	-63.3	5.4	-43.6	-6.6	-46.9	1.1	-46.3
LDL-C (on treatment)[b]	1.4	-64.2	5.3	-44.0	-6.6	-46.9	1.7	-47.6
Week 24								

LDL-C (ITT)[a]	0.8	-61.0[c]	7.1	-48.8[d]	-6.6	-45.7[e]	-2.3	-48.2[f]
LDL-C (on treatment)[b]	0.7	-62.8	6.8	-49.3	-6.6	-45.5	-0.8	-50.7
Non-HDL-C	0.7	-51.6	7.4	-42.8	-6.2	-41.9	-1.6	-39.1
Apo B	1.2	-52.8	1.9	-41.7	-8.7	-39.0	-0.9	-36.7
Total-C	-0.3	-37.8	5.5	-31.2	-4.8	-33.2	-2.9	-27.9
Lp(a)	-3.7	-29.3	-8.5	-26.9	-8.7	-23.5	-5.9	-20.5
TG	1.8	-15.6	4.3	-9.8	-1.9	-10.5	-5.4	-6.0
HDL-C	-0.6	4.0	0.2	7.8	3.9	7.5	-3.8	3.5
Apo A-1	1.2	4.0	-0.4	4.2	2.0	5.6	-2.5	3.3

Mean percent change from baseline in ezetimibe-controlled studies

	On background statin		**Without background statin**			
	COMBO II (N=707)		**ALTERNATIVE (N=248)**		**MONO (N=103)**	
	Ezetimibe	**Alirocumab**	**Ezetimibe**	**Alirocumab**	**Ezetimibe**	**Alirocumab**
Number of patients	240	467	122	126	51	52
Mean baseline LDL-C in mg/dL (mmol/L)	104.5 (2.71)	108.3 (2.81)	194.2 (5.03)	191.1 (5.0)	138.3 (3.58)	141.1 (3.65)
Week 12						
LDL-C (ITT)[a]	-21.8	-51.2	-15.6	-47.0	-19.6	-48.1
LDL-C (on treatment)[b]	-22.7	-52.4	-18.0	-51.2	-20.4	-53.2
Week 24						
LDL-C (ITT)[a]	-20.7	-50.6[g]	-14.6	-45.0[h]	-15.6	-47.2[i]
LDL-C (on treatment)[b]	-21.8	-52.4	-17.1	-52.2	-17.2	-54.1
Non-HDL-C	-19.2	-42.1	-14.6	-40.2	-15.1	-40.6
Apo B	-18.3	-40.7	-11.2	-36.3	-11.0	-36.7
Total-C	-14.6	-29.3	-10.9	-31.8	-10.9	-29.6
Lp(a)	-6.1	-27.8	-7.3	-25.9	-12.3	-16.7
TG	-12.8	-13.0	-3.6	-9.3	-10.8	-11.9
HDL-C	0.5	8.6	6.8	7.7	1.6	6.0
Apo A-1	-1.3	5.0	2.9	4.8	-0.6	4.7

[a] ITT analysis – intent-to-treat population, includes all lipid data throughout the duration of the study irrespective of adherence to the study treatment.

[b] On-treatment analysis – analysis restricted to the time period that patients actually received treatment.

The % LDL-C reduction at week 24 corresponds to a mean absolute change of:

[c] -74.2 mg/dL (-1.92 mmol/L); [d] -71.1 mg/dL (-1.84 mmol/L); [e] -90.8 mg/dL (-2.35 mmol/L); [f] -50.3 mg/dL (-1.30 mmol/L); [g] -55.4 mg/dL (1.44 mmol/L) ;[h] -84.2 mg/dL (-2.18 mmol/L); [i] -66.9 mg/dL (-1.73 mmol/L)

Every 4 week (Q4W) dosing regimen

CHOICE I study

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

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

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

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

Clinical efficacy and safety in prevention of cardiovascular events

ODYSSEY OUTCOMES study

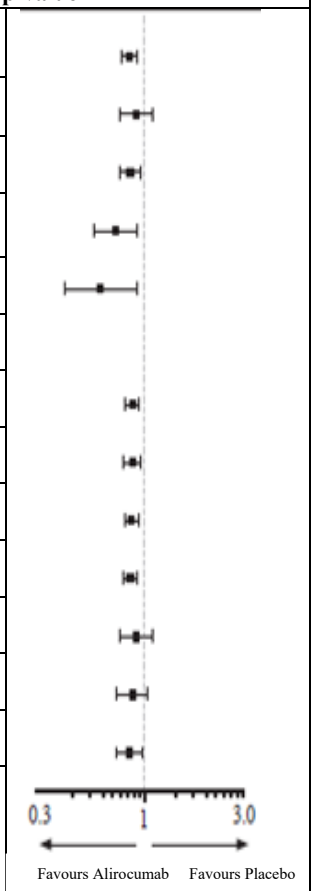
A multicentre, double-blind, placebo-controlled trial included 18,924 adult patients (9,462 alirocumab; 9,462 placebo) followed for up to 5 years. Patients had experienced an acute coronary syndrome (ACS) event 4 to 52 weeks prior to randomization and were treated with a lipid-modifying-therapy (LMT)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

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

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

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

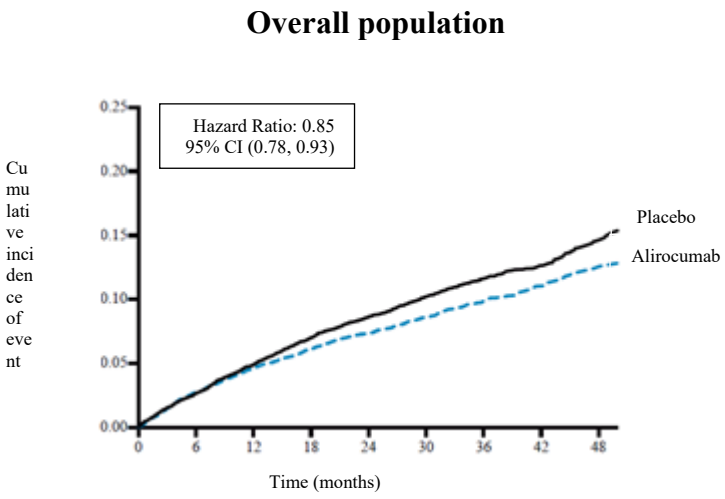
Endpoint	Number of events		Hazard ratio (95% CI) p-value
	Alirocumab N=9,462 n (%)	Placebo N=9,462 n (%)	
Primary endpoint (MACE-plus[a])	903 (9.5%)	1052 (11.1%)	0.85 (0.78, 0.93) 0.0003
CHD death	205 (2.2%)	222 (2.3%)	0.92 (0.76, 1.11) 0.38
Non-fatal MI	626 (6.6%)	722 (7.6%)	0.86 (0.77, 0.96) 0.006[f]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



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

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

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



Neurocognitive function

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

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

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

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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

Biotransformation

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

Elimination

Two elimination phases were observed for alirocumab. At low concentrations, the elimination is predominately through saturable binding to target (PCSK9), while at higher concentrations the elimination of alirocumab is largely through a non-saturable proteolytic pathway.

Based on a population pharmacokinetic analysis, the median apparent half-life of alirocumab at steady state was 17 to 20 days in patients receiving alirocumab as monotherapy at subcutaneous doses of either 75 mg Q2W or 150 mg Q2W. When co-administered with a statin, the median apparent half-life of alirocumab was 12 days.

Linearity/non-linearity

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

Special populations

Elderly

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

Gender

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

Race

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

Body weight

Body weight was identified as one significant covariate in the final population PK model impacting alirocumab pharmacokinetics. Alirocumab exposure (AUC0-14d) at steady state at both the 75 and 150 mg Q2W dosing regimen was decreased by 29% and 36% in patients weighing more than 100 kg as compared to patients weighing between 50 kg and 100 kg. This did not translate into a clinically meaningful difference in LDL-C lowering.

Hepatic impairment

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

Renal impairment

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

Pharmacokinetic/pharmacodynamic relationship(s)

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

5.3 Preclinical safety data

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

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

There were no adverse effects on surrogate markers of fertility (e.g. estrous cyclicity, testicular volume, ejaculate volume, sperm motility, or total sperm count per ejaculate) in monkeys, and no alirocumab-related anatomic pathology or histopathology findings in reproductive tissues in any rat or monkey toxicology study.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Sucrose
L-Histidine/L-Histidine monohydrochloride monohydrate
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:

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

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

Pre-filled pen 75 mg/ml

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

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

Pre-filled pen 150 mg/ml

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

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

Pre-filled pen 300 mg/2 ml

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

Pack size:
1 or 3 pre-filled pens.

Pre-filled syringe 75 mg/ml

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

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

Pre-filled syringe 150 mg/ml

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

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

Not all presentations and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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

7. MANUFACTURER

Sanofi-aventis groupe, France

8. LICENSE NUMBER

Praluent 150 mg/ml: 156-09-34568
Praluent 75 mg/ml: 156-08-34583

9. REGISTRATION HOLDER

Sanofi-Aventis Israel ltd. 10 Beni Gaon, Netanya.

Revised in May 2023 according to MoH guidelines.

עלון לצרכן לפי תקנות הרוקחים
(תכשירים) התשמ"ו - 1986
התרופה משווקת על פי מרשם רופא בלבד

פראלואנט 75 מ"ג/מ"ל
תמיסה להזרקה תת עורית
פראלואנט 150 מ"ג/מ"ל
תמיסה להזרקה תת עורית

חומר פעיל:
- פראלואנט 75 מ"ג/מ"ל - כל עט/מזרק מוכן לשימוש מכיל 75 מ"ג של אלירוקומאב alirocumab 75 mg.
- פראלואנט 150 מ"ג/מ"ל - קיים בשני נפחים - 1 מ"ל, 2 מ"ל. כל עט/מזרק מוכן לשימוש בנפח של 1 מ"ל מכיל 150 מ"ג של אלירוקומאב alirocumab 150 mg.
  כל עט מוכן לשימוש בנפח של 2 מ"ל מכיל 300 מ"ג של אלירוקומאב alirocumab 300 mg.

חומרים בלתי פעילים: ראה סעיף 6.

קרא בעיון את העלון עד סופו בטרם תשתמש בתרופה.
שמור על עלון זה, ייתכן ותצטרך לקרוא בו שוב.
עלון זה מכיל מידע תמציתי על התרופה.
אם יש לך שאלות נוספות, פנה אל הרופא, הרוקח או האחות.
תרופה זו נרשמה עבורך. אל תעביר אותה לאחרים. היא עלולה להזיק להם אפילו אם נראה לך כי מצבם הרפואי דומה.
פראלואנט אינו מיועד לשימוש בילדים ומתבגרים מתחת לגיל 18 שנים.

1. למה מיועד פראלואנט?
- לטיפול במבוגרים עם רמות כולסטרול גבוהות בדם (הסובלים מהיפרכולסטרולמיה ראשונית [משפחתית הטרוזיגוטית או לא משפחתית] או דיסליפידמיה מעורבת) בשילוב עם תזונה מותאמת.
- לטיפול במבוגרים עם רמות כולסטרול גבוהות בדם ועם מחלה קרדיווסקולרית על מנת להפחית את הסיכון הקרדיווסקולרי.

התרופה ניתנת:
* בשילוב עם תרופה מקבוצת הסטטינים או בשילוב עם תרופה מקבוצת הסטטינים ותרופות נוספות להורדת רמות שומנים בדם, במטופלים בהם המינון המקסימאלי הנסבל של תרופה מקבוצת הסטטינים אינו מוריד את רמות הכולסטרול בדם בצורה מספקת
או
כטיפול יחיד (פראלואנט בלבד) או בשילוב עם תרופות נוספות להורדת רמות שומנים בדם במטופלים בהם תרופות מקבוצת הסטטינים לא נסבלות או לא ניתן להשתמש בהן.

קבוצה תרפויטית:
אלירוקומאב הינו נוגדן חד שבטי אנושי המסייע להורדת רמות הכולסטרול בדם.
פראלואנט עוזר להוריד רמות של הכולסטרול ה"רע" שלך (הנקרא גם LDL כולסטרול).
פראלואנט חוסם את החלבון PCSK9.
* PCSK9 הינו חלבון המופרש על ידי תאי כבד.
* הכולסטרול ה"רע" בדרך כלל מפונה מדמך על ידי קישור לקולטנים ספציפיים ("תחנות עגינה") בכבד שלך.
* PCSK9 מקטין את מספר הקולטנים האלו בכבד - מה שגורם לכולסטרול ה"רע" שלך להיות גבוה יותר מהנדרש.
  פראלואנט חוסם את PCSK9 ועל ידי כך מעלה את מספר הקולטנים הזמינים לסייע בהורדת הכולסטרול ה"רע" שלך.

<MAT>892044

2. לפני השימוש בתרופה
אין להשתמש בתרופה:
אם הנך רגיש לאלירוקומאב או לאחד מהמרכיבים האחרים של תרופה זו (ראה סעיף 6).

אזהרות מיוחדות הנוגעות לשימוש בתרופה
שוחח עם הרופא, הרוקח או האחות לפני תחילת השימוש בפראלואנט.
אם מתפתחת לך תגובה אלרגית חמורה, הפסק לקחת פראלואנט ופנה לרופא מיד. לפעמים התרחשו תגובות אלרגיות חמורות כמו רגישות יתר, כולל אנגיואדמה (קשיי נשימה, או התנפחות של הפנים, השפתיים, הגרון או הלשון), nummular eczema (כתמים אדמומיים על העור, לפעמים עם שלפוחיות) ודלקת כלי דם על רקע רגישות יתר (hypersensitivity vasculitis) - צורה מיוחדת של תגובת רגישות יתר עם סימפטומים כמו שלשול, עם פריחה או נקודות סגולות על העור.
למידע על תגובות אלרגיות שעלולות לקרות בזמן נטילת פראלואנט ראה סעיף 4.
לפני השימוש בתרופה ספר לרופא שלך אם אתה סובל ממחלת כליה או כבד, כיוון שפראלואנט נבדק במספר קטן של מטופלים עם מחלת כליות חמורה ולא נבדק במטופלים עם מחלת כבד חמורה.

ילדים ומתבגרים
פראלואנט אינה מיועדת לילדים ולמתבגרים מתחת לגיל 18.
הבטיחות והיעילות לא הוכחו בילדים ובמתבגרים מתחת לגיל 18.

אם אתה לוקח או אם לקחת לאחרונה תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח.

היריון והנקה
אם את בהיריון או מיניקה, חושבת שאת עשויה להיות בהיריון או מתכננת היריון, התייעצי עם הרופא או עם הרוקח שלך לפני לקיחת תרופה זו.
פראלואנט אינו מומלץ במהלך היריון או בתקופת הנקה.

נהיגה ושימוש במכונות
תרופה זו לא צפויה להשפיע על יכולתך לנהוג או להשתמש במכונות.

3. כיצד להשתמש בתרופה?
תמיד יש להשתמש בדיוק לפי הוראות הרופא. עליך לבדוק עם הרופא או הרוקח אם אינך בטוח.

כמה להזריק
הרופא שלך יקבע את המינון הנכון עבורך ואת תדירות ההזרקה הנכונה (75 מ"ג או 150 מ"ג כל שבועיים או 300 מ"ג פעם ב- 4 שבועות [פעם בחודש]).
במהלך הטיפול הרופא יבדוק את רמות הכולסטרול שלך ועשוי להתאים את המינון בהתאם (להעלות או להוריד).
לפני כל הזרקה בדוק את התווית, וודא ששם התרופה והמינון נכונים.

מתי להזריק
יש להזריק פראלואנט אחת לשבועיים (למינון של 75 מ"ג או 150 מ"ג), או פעם ב- 4 שבועות (פעם בחודש) (למינון של 300 מ"ג). על מנת להזריק מנה של 300 מ"ג, יש לבצע זריקה אחת של 300 מ"ג, או שתי זריקות של 150 מ"ג אחת אחרי השנייה, בשני מקומות הזרקה שונים.

לפני ההזרקה
יש לאפשר לפראלואנט להתחמם לטמפרטורת החדר לפני השימוש.
קרא את "הוראות השימוש" המפורטות לפני שתזריק פראלואנט.

מקום ההזרקה
פראלואנט מוזרק מתחת לעורך לירך, לבטן או לזרוע העליונה.

הוראות שימוש
לפני השימוש הראשון, הרופא שלך, האחות או הרוקח יראו לך כיצד להזריק פראלואנט בצורה נכונה.
- קרא תמיד ביסודיות את "**הוראות השימוש**" שבאריזה.
- עליך להשתמש בעט/מזרק כפי שמתואר ב"**הוראות השימוש**".

אם השתמשת ביותר פראלואנט מהנדרש
אם השתמשת ביותר פראלואנט מהנדרש, פנה לרופא, לרוקח או לאחות.

אם שכחת להשתמש בפראלואנט
אם שכחת את המנה של פראלואנט, הזרק אותה מיד כשאתה יכול. את המנה הבאה **הזרק לפי לוח הזמנים הרגיל**. זה יחזיר אותך ללוח הזמנים המקורי. אם אינך בטוח מתי להזריק פראלואנט, היוועץ ברופא, ברוקח או באחות.
אין להזריק מנה כפולה כפיצוי על מנה שנשכחה.

אם הפסקת להשתמש בפראלואנט
אל תפסיק להשתמש בפראלואנט בלי להיוועץ ברופא. הפסקת השימוש עלולה לגרום לעליית רמת הכולסטרול שלך.

<u>אין ליטול תרופות בחושך</u>! בדוק התווית והמנה <u>בכל פעם</u> שהנך נוטל תרופה. הרכב משקפיים אם הנך זקוק להם.
אם יש לך שאלות נוספות בנוגע לשימוש בתרופה היוועץ ברופא, ברוקח או באחות.

4. תופעות לוואי
כמו בכל תרופה, השימוש בפראלואנט עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. ייתכן ולא תסבול מאף אחת מהן.
אם אתה מפתח תגובה אלרגית חמורה, הפסק את השימוש בפראלואנט ופנה לרופא מיד.
נצפו לפעמים (עד מטופל אחד מתוך 1000) תגובות אלרגיות חמורות הכוללות: רגישות יתר (קשיי נשימה), nummular eczema - כתמים אדמומיים על העור, לפעמים עם שלפוחיות ודלקת כלי דם על רקע רגישות יתר (hypersensitivity vasculitis) - צורה מיוחדת של תגובת רגישות יתר עם סימפטומים כמו שלשול, עם פריחה או נקודות סגולות על העור.

<u>תופעות לוואי נוספות:</u>
<u>תופעות לוואי שכיחות</u> (common) - תופעות שעשויות להופיע בעד מטופל 1 מתוך 10:
- אדמומיות, גרד, נפיחות, כאב/רגישות במקום ההזרקה (תגובה מקומית במקום ההזרקה).
- סימפטומים של דלקת בדרכי נשימה עליונות כמו כאבי גרון, נזלת, התעטשות.
- גרד (פרוריטיס).

<u>תופעות לוואי נדירות</u> (rare) - תופעות שעשויות להופיע בעד מטופל 1 מתוך 1000:
- בליטות אדומות ומגרדות או סרפדת (urticaria).

<u>שכיחות לא ידועה</u>:
תופעות הלוואי הבאות דווחו מאז שיווקו של פראלואנט, אך שכיחותן לא ידועה:
- מחלה דמוית שפעת.
- קשיי נשימה, או התנפחות של הפנים, השפתיים, הגרון או הלשון (אנגיואדמה).

אם הופיעה תופעת לוואי, אם אחת מתופעות הלוואי מחמירה, או אם אתה סובל מתופעת לוואי שלא הוזכרה בעלון, עליך להתייעץ עם הרופא.

ניתן לדווח על תופעות לוואי למשרד הבריאות באמצעות לחיצה על הקישור "דיווח על תופעות לוואי עקב טיפול תרופתי" שנמצא בדף הבית של אתר משרד הבריאות (www.health.gov.il) המפנה לטופס המקוון לדיווח על תופעות לוואי, או ע"י כניסה לקישור: https://sideeffects.health.gov.il

5. כיצד לאחסן את התרופה
<u>מנע הרעלה</u>! תרופה זו וכל תרופה אחרת יש לשמור במקום סגור מחוץ להישג ידם וטווח ראייתם של ילדים ו/או תינוקות ועל ידי כך תמנע הרעלה.

תרופה זו נרשמה לטיפול במחלתך, בחולה אחר, היא עלולה להזיק. אל תיתן תרופה זו לקרוביך, שכניך או מכריך.
אין להשתמש בתרופה אחרי תאריך התפוגה (exp. date) המופיע על גבי האריזה ועל גבי העט/המזרק. תאריך התפוגה מתייחס ליום האחרון של אותו חודש.
אחסן במקרר (2°C-8°C). אל תקפיא. יש לאחסן את העטים/המזרקים המוכנים לשימוש בתוך האריזה המקורית על מנת להגן מאור.
במידת הצורך ניתן לשמור עטים/מזרקים בודדים מחוץ למקרר מתחת ל- 25°C למשך עד 30 יום מקסימום. יש להגן מאור. לאחר ההוצאה מהמקרר, יש להשתמש בפראלואנט תוך 30 יום או להשליך.
אל תשתמש בתרופה אם התמיסה נראית בצבע לא תקין, עכורה או מכילה חלקיקים או גושים הנראים לעין.
אין לאחסן תרופות שונות באותה אריזה.
לאחר השימוש הכנס את העט/מזרק למכל עמיד לדקירות. שאל את הרופא, הרוקח או האחות איך להשליך את המכל. אל תמחזר את המכל.
אין להשליך תרופות באשפה הביתית או לתוך הביוב הביתי. שאל את הרוקח שלך איך להשליך תרופות שאינך זקוק להן יותר. אמצעים אלו יעזרו להגן על הסביבה.

6. מידע נוסף
נוסף על החומר הפעיל, כל עט/מזרק מכיל גם את החומרים הבלתי פעילים הבאים:
Sucrose, L-Histidine/L-Histidine monohydrochloride monohydrate, Polysorbate 20, Water for injection.

כיצד נראית התרופה ומה תוכן האריזה:
פראלואנט זו תמיסה להזרקה, צלולה, חסרת צבע עד צבע צהוב בהיר, בתוך עט/מזרק מוכן לשימוש.
פראלואנט 75 מ"ג/מ"ל: כל עט מוכן לשימוש עם הכפתור הירוק/מזרק מוכן לשימוש עם בוכנה ירוקה מכיל 1 מ"ל תמיסה, ומשחרר מנה אחת של 75 מ"ג אלירוקומאב.
קיימות אריזות של 1, 2 או 6 עטים/מזרקים, לא כל גדלי האריזה משווקים.
פראלואנט 150 מ"ג/מ"ל: קיים בשני נפחים – 1 מ"ל, 2 מ"ל.
<u>1 מ"ל</u>:
כל עט מוכן לשימוש עם הכפתור האפור/מזרק מוכן לשימוש עם בוכנה אפורה מכיל 1 מ"ל תמיסה, ומשחרר מנה אחת של 150 מ"ג אלירוקומאב.
קיימות אריזות של 1, 2 או 6 עטים/מזרקים, לא כל גדלי האריזה משווקים.
<u>2 מ"ל</u>:
כל עט מוכן לשימוש ללא כפתור מכיל 2 מ"ל תמיסה, ומשחרר מנה אחת של 300 מ"ג אלירוקומאב.
קיימות אריזות של 1 או 3 עטים, לא כל גדלי האריזה משווקים.
עלון זה לא כולל את כל המידע על התכשירים. אם יש לך שאלה כלשהי או אינך בטוח בדבר מה, אנא פנה לרופא.
שם בעל הרישום, היבואן וכתובתו: סאנופי-אוונטיס ישראל בע"מ, רחוב בני גאון 10, נתניה.
מספר רישום התרופה בפנקס התרופות הממלכתי במשרד הבריאות:
פראלואנט 75 מ"ג/מ"ל: 156-08-34583
פראלואנט 150 מ"ג/מ"ל: 156-09-34568
לשם הפשטות ולהקלת הקריאה, עלון זה נוסח בלשון זכר. על אף זאת, התרופה מיועדת לבני שני המינים.
נערך במאי 2023 בהתאם להנחיות משרד הבריאות.

PRAL-75mg-150mg-sol-for-inj-PIL-1.0-IFU-300mg/2ml

PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE <u>PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986</u>
The medicine is dispensed with a doctor's prescription only

PRALUENT 75 MG/ML
Solution for subcutaneous injection
PRALUENT 150 MG/ML
Solution for subcutaneous injection

Active ingredient:
- <u>Praluent 75 mg/ml</u> – each pre-filled pen/syringe contains 75 mg alirocumab.
- <u>Praluent 150 mg/ml</u> – available in two volumes – 1 ml, 2 ml. Each 1 ml pre-filled pen/syringe contains 150 mg alirocumab. Each 2 ml pre-filled pen contains 300 mg alirocumab.

Inactive ingredients: see section 6.

Read this leaflet carefully in its entirety before using the medicine.
Keep this leaflet; you may need to read it again.
This leaflet contains concise information about the medicine.
If you have further questions, refer to the doctor, pharmacist or nurse.
This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.
Praluent is not intended for use in children and adolescents under 18 years of age.

1. WHAT PRALUENT IS INTENDED FOR?
- For treatment of adults with high cholesterol levels in their blood (suffering from primary hypercholesterolemia [heterozygous familial or non-familial] or mixed dyslipidemia) in combination with a suitable diet.
- For treatment of adults with high cholesterol levels in their blood and with a cardiovascular disease, to reduce cardiovascular risk.

It is given:
* Together with a statin or with a statin and other blood lipid-lowering medicines if the maximum tolerated dose of a statin does not lower levels of cholesterol sufficiently
or
as a monotherapy (Praluent only) or together with other blood lipid-lowering medicines when statins are not tolerated or cannot be used.

Therapeutic group:
Alirocumab is a human monoclonal antibody that helps lower blood cholesterol levels.
Praluent helps lower your levels of "bad" cholesterol (also called LDL cholesterol).
Praluent blocks the 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 your "bad" cholesterol.

2. BEFORE USING THE MEDICINE
Do not use this medicine:
if you are allergic to alirocumab or to any of the other ingredients in this medicine (see section 6).

Special warnings regarding use of the medicine
Talk to the doctor, pharmacist or nurse before beginning using Praluent.
If you develop a serious allergic reaction, stop using Praluent and talk to your doctor right away. Sometimes, serious allergic reactions such as hypersensitivity, including angioedema (difficulties breathing, or swelling of the face, lips, throat or tongue), nummular eczema (reddish skin spots, sometimes with blisters), and hypersensitivity vasculitis (a specific form of hypersensitivity reaction with symptoms such as diarrhea, with a rash, or purple-colored skin spots on the skin) have occurred.
For information on 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 a few patients with severe kidney disease and not in patients with severe liver disease.

Children and adolescents
Praluent is not intended for children and adolescents under 18 years of age. The safety and the effectiveness have not been proven in children and adolescents under 18 years of age.

If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist.

Pregnancy and breastfeeding
If you are pregnant or breastfeeding, think you may be pregnant or are planning pregnancy, consult the doctor or pharmacist before taking this medicine.
Praluent is not recommended during pregnancy or breastfeeding.

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

3. HOW SHOULD YOU USE THE MEDICINE?
Always use exactly in accordance with the doctor's instructions. Check with the doctor or pharmacist if you are not sure.

How much to inject
Your doctor will determine the proper dose for you and how often to inject (75 mg or 150 mg every two weeks, or 300 mg once every 4 weeks [monthly]).
Your doctor will check your cholesterol levels and may adjust the dose (up or down) accordingly.
Check the label before each injection; make sure that the name of the medicine and the strength are correct.

When to inject
Inject Praluent once every two weeks (for the 75 mg or 150 mg dose), or once every 4 weeks (monthly) (for the 300 mg dose). In order to inject a dose of 300 mg, administer one injection of 300 mg, or two injections of 150 mg one after the other, at two different injection sites.

Before you inject
Praluent should be allowed to warm to room temperature prior to use.
Read the detailed "Instructions for Use" before you inject Praluent.

Injection site
Praluent is injected under your skin into the thigh, abdomen or upper arm.

892044/2

Instructions for use
Before you use the pen/syringe for the first time, your doctor, pharmacist or nurse will show you how to inject Praluent correctly.
- Always read carefully the "**Instructions for Use**" provided in the package.
- Always use the pen/syringe as described in the "**Instructions for Use**".

If you use more Praluent than you should
If you use more Praluent than you should, refer to a 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 **according to the regular schedule**. This will keep you on the original schedule. If you are not sure when to inject Praluent, consult the doctor, pharmacist or nurse.
Do not inject a double dose to compensate for a missed dose.

If you stop using Praluent
Do not stop using Praluent without consulting the doctor. If you stop using Praluent, your cholesterol levels can increase.
<u>Do not take medicines in the dark</u>! Check the label and the dose <u>each time</u> you take a medicine. Wear glasses if you need them.
If you have any further questions regarding use of the medicine, consult a doctor, pharmacist or nurse.

4. SIDE EFFECTS
As with any medicine, use of Praluent may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.
If you develop a serious allergic reaction, stop using Praluent and refer to your doctor right away.
Sometimes (up to 1 in 1,000 patients) 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 hypersensitivity reaction with symptoms such as diarrhea, with a rash, or purple-colored skin spots on the skin) have occurred.

<u>Additional side effects</u>:
<u>Common side effects</u> - effects that may occur in up to 1 patient in 10:
- redness, itching, swelling, pain/tenderness where the medicine was injected (local injection site reaction).
- upper respiratory tract symptoms such as sore throat, runny nose, sneezing.
- itching (pruritus).

<u>Rare side effects</u> - effects that may occur in up to 1 patient in 1000:
- red and itchy raised bumps or hives (urticaria).

- <u>Unknown frequency</u>:

The following side effects have been reported since the marketing of Praluent, but how often they occur is not known:
- flu-like illness.
- difficulties breathing, or swelling of the face, lips, throat or tongue (angioedema).

If a side effect occurs, if one of the side effects worsens, or if you are suffering from a side effect not mentioned in the leaflet, consult the doctor.

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il

5. HOW SHOULD THE MEDICINE BE STORED?
<u>Avoid poisoning</u>! This medicine and any other medicine must be kept in a safe place out of the reach and sight of children and/or infants in order to avoid poisoning.
This medicine was prescribed to treat your ailment; in another patient, it can cause harm. Do not give this medicine to your relatives, neighbors or acquaintances.
Do not use the medicine after the expiry date (exp. date) that appears on the package and on the pen/syringe. The expiry date refers to the last day of that month.
Store in a refrigerator (2°C-8°C). Do not freeze. Keep the pre-filled pens/syringes in the original package in order to protect from light.
If needed, individual pens/syringes may be kept outside the refrigerator below 25°C for a maximum of 30 days. Protect from light. After removal from the refrigerator, Praluent must be used within 30 days or discarded.
Do not use this medicine if the solution looks discolored, cloudy, or if it contains visible flakes or particles.
Do not store different medications in the same package.
After use, put the pen/syringe into a puncture-resistant container. Ask the doctor, pharmacist or nurse how to throw away the container. Do not recycle the container.
Do not throw away medicines via household waste or wastewater. Ask your pharmacist how to throw away medicines you no longer need. These measures will help protect the environment.

6. FURTHER INFORMATION
In addition to the active ingredient, each pen/syringe also contains the following inactive ingredients:
Sucrose, L-Histidine/L-Histidine monohydrochloride monohydrate, Polysorbate 20, Water for injection.

What the medicine looks like and the contents of the package:
Praluent is a clear, colorless to light yellow solution provided in a pre-filled pen/syringe.
Praluent 75 mg/ml: Each pre-filled pen with a green button/pre-filled syringe with a green plunger contains 1 ml of solution, and releases a single dose of 75 mg alirocumab.
It is available in pack size of 1, 2 or 6 pre-filled pens/syringes; not all pack sizes are marketed.
Praluent 150 mg/ml: Available in two volumes - 1 ml, 2 ml.
<u>1 ml</u>:
Each pre-filled pen with a gray button/pre-filled syringe with a gray plunger contains 1 ml of solution, and releases a single dose of 150 mg alirocumab.
It is available in pack size of 1, 2 or 6 pre-filled pens/syringes; not all pack sizes are marketed.
<u>2 ml</u>:
Each pre-filled pen without a button contains 2 ml of solution, and releases a single dose of 300 mg alirocumab.
It is available in pack size of 1 or 3 pre-filled pens. Not all pack sizes are marketed.

This leaflet does not contain all the information about the preparations. If you have any question or are uncertain about something, please refer to a doctor.
License holder name and importer and its address: sanofi-aventis Israel ltd., 10 Beni Gaon Street, Netanya.
Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Praluent 75 mg/ml: 156-08-34583
Praluent 150 mg/ml: 156-09-34568
Revised in May 2023 according to MOH guidelines.

PRAL-75mg-150mg-sol-for-inj-PIL-1.0-IFU-300mg/2ml

نشرة للمستهلك بموجب أنظمة الصيدلة
<u>(مستحضرات) - 1986</u>
يسوّق الدواء بموجب وصفة طبيب فقط

پرالوِئنت 75 ملغ/ملل
محلول للحقن تحت الجلد
پرالوِئنت 150 ملغ/ملل
محلول للحقن تحت الجلد

المادة الفعالة:
- <u>پرالوئنت 75 ملغ/ملل</u> - كل قلم/محقنة جاهزة للإستعمال يحتوي على 75 ملغ من أليروكوماب alirocumab 75 mg.
- <u>پرالوئنت 150 ملغ/ملل</u> - يتوفر بحجمين - 1 ملل، 2 ملل.
  كل قلم/محقنة جاهزة للإستعمال بحجم 1 ملل يحتوي على 150 ملغ من أليروكوماب alirocumab 150 mg.
  كل قلم جاهز للإستعمال بحجم 2 ملل يحتوي على 300 ملغ أليروكوماب alirocumab 300 mg.

المواد غير الفعالة: أنظر الفقرة 6.

إقرأ النشرة بتمعن حتى نهايتها قبل إستعمالك للدواء.
إحفظ هذه النشرة، من الجائز أن تحتاج لقراءتها ثانية.
تحتوي هذه النشرة على معلومات موجزة عن الدواء.
إذا توفرت لديك أسئلة إضافية، راجع الطبيب، الصيدلي أو الممرضة.
وُصف هذا الدواء من أجلك. لا تعطيه للآخرين. فهو قد يضرهم حتى ولو بدا لك أن حالتهم الطبية مشابهة لحالتك.
پرالوئنت غير مخصص للإستعمال لدى الأطفال والمراهقين دون عمر 18 سنة.

1) لأي غرض مخصص پرالوئنت؟
- لمعالجة الكبار الذين لديهم نسب مرتفعة من الكولسترول في الدم (الذين يعانون من فرط كولسترول الدم الأولي [العائلي متباين الزيجوت أو غير العائلي] أو من عسر شحميات الدم المختلط) بمشاركة تغذية تمت ملاءمتها.
- لعلاج الكبار الذين لديهم نسب مرتفعة من الكولسترول في الدم ولديهم مرض قلبي وعائي وذلك من أجل تقليل الخطورة على القلب والأوعية الدموية.

يعطى الدواء:
* بمشاركة دواء من فصيلة الستاتينات أو بمشاركة دواء من فصيلة الستاتينات وأدوية إضافية لخفض نسب الشحوم في الدم، لدى متعالجين الذين لا يخفض لديهم المقدار الدوائي الأعظمي الذي يمكن تحمله لدواء من فصيلة الستاتينات بشكل كاف من نسب الكولسترول في الدم
أو
كعلاج منفرد (پرالوئنت لوحده) أو بمشاركة أدوية إضافية لخفض نسب الشحوم في الدم لدى متعالجين لا يمكنهم تحمل أدوية من فصيلة الستاتينات أو لا يمكن إستعمالها لديهم.

الفصيلة العلاجية:
أليروكوماب هو ضد بشري أحادي النسيلة يساعد على خفض نسب الكولسترول في الدم.
يساعد پرالوئنت على خفض نسب الكولسترول "السيء" لديك (المسمى أيضاً LDL كولسترول).
پرالوئنت يحجب البروتين PCSK9.
* PCSK9 هو عبارة عن پروتين يفرز من قبل خلايا الكبد.
* يتم عادة طرح الكولسترول "السيء" من دمك بواسطة إرتباطه بمستقبلات معينة ("محطات إرساء") في كبدك.
* PCSK9 يقلل من عدد تلك المستقبلات في الكبد - الأمر الذي يجعل الكولسترول "السيء" لديك مرتفعاً أكثر من المطلوب.
  پرالوئنت يحجب PCSK9 وبذلك يزيد من عدد المستقبلات المتوفرة للمساعدة على خفض الكولسترول "السيء" لديك.

892044/3

2) قبل إستعمال الدواء
لا يجوز إستعمال الدواء:
إذا كنت حساساً لأليروكوماب أو لأحد المركبات الأخرى لهذا الدواء (أنظر الفقرة 6).

تحذيرات خاصة تتعلق بإستعمال الدواء
قبل بدء إستعمال پرالوئنت، تحدث مع الطبيب، الصيدلي أو الممرضة.
إذا تطور لديك رد فعل تحسسي خطير، توقف عن إستعمال پرالوئنت وتوجه في الحال إلى الطبيب. حدثت أحياناً ردود فعل تحسسية خطيرة مثل فرط حساسية، بما في ذلك وذمة وعائية (صعوبات في التنفس، أو إنتفاخ الوجه، الشفتين، الحنجرة أو اللسان)، nummular eczema (إكزيما درهمية) (بقع حمراء على الجلد، أحياناً مع حويصلات) وإلتهاب الأوعية الدموية على خلفية فرط الحساسية (hypersensitivity vasculitis) - شكل خاص لرد فعل تحسسي مفرط مع أعراض مثل إسهال، مع طفح أو نقاط بنفسجية على الجلد.
أنظر الفقرة 4 لمعلومات عن ردود الفعل التحسسية التي قد تحدث أثناء فترة إستعمال پرالوئنت.
قبل إستعمال الدواء بلغ طبيبك إذا كنت تعاني من مرض في الكلية أو في الكبد، وذلك لأنه تم فحص پرالوئنت لدى عدد قليل من المتعالجين الذين لديهم مرض كلوي شديد ولم يتم فحصه لدى متعالجين لديهم مرض كبدي شديد.

الأطفال والمراهقون
پرالوئنت غير مخصص للأطفال وللمراهقين دون عمر 18 سنة.
لم تثبت السلامة والنجاعة لدى الأطفال والمراهقين دون عمر 18 سنة.

إذا كنت تستعمل أو إذا إستعملت مؤخراً أدوية أخرى بما في ذلك أدوية بدون وصفة طبية وإضافات غذائية، إحك للطبيب أو الصيدلي عن ذلك.

الحمل والإرضاع
إذا كنت في فترة الحمل أو مرضعة، تعتقدين بأنه من شأنك أن تكوني حاملاً أو تخططين للحمل، إستشيري الطبيب أو الصيدلي الخاص بك قبل إستعمال هذا الدواء.
لا يوصى بإستعمال پرالوئنت خلال فترة الحمل أو خلال فترة الرضاعة.

السياقة وإستعمال الماكنات
من غير المتوقع أن يؤثر هذا الدواء على قدرتك على السياقة أو إستعمال الماكنات.

3) كيفية إستعمال الدواء؟
يجب دائماً الإستعمال حسب تعليمات الطبيب بالضبط. عليك الإستيضاح من الطبيب أو الصيدلي إذا لم تكن واثقاً.

كم تحقن
يحدد طبيبك المقدار الدوائي الصحيح من أجلك ووتيرة الحقن الصحيحة (75 ملغ أو 150 ملغ كل أسبوعين أو 300 ملغ مرة كل 4 أسابيع [مرة في الشهر]).
يقوم الطبيب خلال فترة العلاج بفحص نسب الكولسترول لديك ومن شأنه أن يقوم بملاءمة المقدار الدوائي وفقاً لذلك (رفع أو خفض المقدار الدوائي).
قبل كل عملية حقن تحقق من الملصقة, وتأكد من صحة إسم الدواء والمقدار الدوائي.

متى تحقن
يجب حقن پرالوئنت مرة كل أسبوعين (لمقدار دوائي قدره 75 ملغ أو 150 ملغ)، أو مرة كل 4 أسابيع (مرة في الشهر) (لمقدار دوائي قدره 300 ملغ).
من أجل حقن مقدار دوائي قدره 300 ملغ، يجب إجراء حقنة واحدة من عيار 300 ملغ، أو حقنتين من عيار 150 ملغ واحدة تلو الأخرى، في مكانين مختلفين للحقن.

قبل الحقن
يجب السماح لـ پرالوئنت أن يدفئ ليبلغ درجة حرارة الغرفة قبل الإستعمال.
إقرأ "تعليمات الإستعمال" المفصلة قبل أن تحقن پرالوئنت.

مكان الحقن
يُحقن پرالوئنت تحت جلدك في الفخذ، البطن أو أعلى الذراع.

تعليمات الإستعمال
قبل الإستعمال الأولي، يريك طبيبك، الممرضة أو الصيدلي كيفية حقن پرالوئنت بشكل صحيح.
- إقرأ دائماً «**تعليمات الإستعمال**» الموجودة في العلبة بدقة.
- يتوجب عليك إستعمال القلم/المحقنة كما هو موصوف في «**تعليمات الإستعمال**».

إذا قمت بإستعمال أكثر من المطلوب من پرالوئنت
إذا قمت بإستعمال أكثر من المطلوب من پرالوئنت، راجع الطبيب، الصيدلي أو الممرضة.

إذا نسيت إستعمال پرالوئنت
إذا نسيت المقدار الدوائي من پرالوئنت، قم بحقنه حالاً متى إستطعت. **إحقن** المقدار الدوائي القادم **بحسب جدول المواعيد الإعتيادي**. بذلك تعود لجدول مواعيد الحقن الأساسي.
إستشر الطبيب، الصيدلي أو الممرضة، إذا كنت غير واثق متى يتوجب عليك حقن پرالوئنت.
لا يجوز حقن مقدار دوائي مضاعف كتعويض عن المقدار الدوائي المنسي.

في حال توقفك عن إستعمال پرالوئنت
لا تتوقف عن إستعمال پرالوئنت بدون إستشارة الطبيب. إن التوقف عن الإستعمال قد يؤدي لإرتفاع نسبة الكولسترول لديك.
<u>لا يجوز إستعمال الأدوية في العتمة</u>! يجب تشخيص طابع الدواء والتأكد من المقدار الدوائي <u>في كل مرة</u> تستعمل فيها دواء. ضع النظارات الطبية إذا لزم الأمر ذلك.
إذا توفرت لديك أسئلة إضافية حول إستعمال الدواء إستشر الطبيب، الصيدلي أو الممرضة.

4) الأعراض الجانبية
كما بكل دواء، إن إستعمال پرالوئنت قد يسبب أعراضاً جانبية عند بعض المستعملين. لا تندهش من قائمة الأعراض الجانبية. من الجائز ألا تعاني أياً منها.
إذا تطور لديك رد فعل تحسسي خطير، توقف عن إستعمال پرالوئنت وتوجه إلى الطبيب في الحال.
في بعض الأحيان تم ملاحظة (لدى حتى متعالج واحد من بين 1000) ردود فعل تحسسية خطيرة تشمل: فرط حساسية (صعوبات في التنفس)، nummular eczema (إكزيما درهمية) - بقع حمراء على الجلد، أحياناً مع حويصلات وإلتهاب الأوعية الدموية على خلفية فرط الحساسية (hypersensitivity vasculitis) - هو شكل خاص من رد فعل لفرط الحساسية مع أعراض مثل إسهال، مع طفح أو نقاط بنفسجية على الجلد.

<u>أعراض جانبية إضافية</u>:
<u>أعراض جانبية شائعة</u> (common) - أعراض من شأنها أن تظهر لدى حتى متعالج 1 من بين 10:
- إحمرار، حكة، إنتفاخ، ألم/حساسية في مكان الحقن (رد فعل موضعي في مكان الحقن).
- أعراض لإلتهاب في الطرق التنفسية العلوية مثل آلام في الحنجرة، رشح، عطاس.
- حكة (pruritus).

<u>أعراض جانبية نادرة</u> (rare) - أعراض من شأنها أن تظهر لدى حتى متعالج 1 من بين 1000:
- بروزات حمراء وحاكة أو شرى (urticaria).

<u>شيوع غير معروف</u>:
الأعراض الجانبية التالية بلغ عنها منذ تسويق پرالوئنت، لكن شيوعها غير معروف:
- مرض يشبه الإنفلوإنزا.
- صعوبات في التنفس، أو إنتفاخ الوجه، الشفتين، الحنجرة أو اللسان (وذمة وعائية).

إذا ظهر عرض جانبي، إذا تفاقمت إحدى الأعراض الجانبية، أو إذا كنت تعاني من عرض جانبي لم يذكر في هذه النشرة، عليك إستشارة الطبيب.
بالإمكان التبليغ عن أعراض جانبية لوزارة الصحة بواسطة الضغط على الرابط «تبليغ عن أعراض جانبية عقب علاج دوائي» الموجود على الصفحة الرئيسية لموقع وزارة الصحة (www.health.gov.il) الذي يوجهك للنموذج المباشر للتبليغ عن أعراض جانبية، أو عن طريق تصفح الرابط:
https://sideeffects.health.gov.il

5) كيفية تخزين الدواء
<u>تجنب التسمم</u>! يجب حفظ هذا الدواء وكل دواء آخر في مكان مغلق بعيداً عن متناول أيدي ومجال رؤية الأطفال و/أو الرضع، وذلك لتفادي إصابتهم بالتسمم.

وُصف هذا الدواء لعلاج مرضك، وهو قد يسبب الضرر لدى مريض آخر. لا تعطِ من هذا الدواء لأقربائك، جيرانك أو معارفك.
لا يجوز إستعمال الدواء بعد إنقضاء تاريخ الصلاحية (exp. date) الذي يظهر على ظهر العلبة وعلى ظهر القلم/المحقنة. يشير تاريخ الصلاحية إلى اليوم الأخير من نفس الشهر.
يجب التخزين في البراد (8-2 درجات مئوية). لا يجوز التجميد.
يجب تخزين الأقلام/المحاقن الجاهزة للإستعمال داخل العلبة الأصلية وذلك لحمايتها من الضوء.
عند الحاجة بالإمكان حفظ أقلام/محاقن منفردة خارج البراد دون 25 درجة مئوية لمدة أقصاها حتى 30 يوماً. يجب الحماية من الضوء. بعد الإخراج من البراد، يجب إستعمال پرالوئنت خلال 30 يوماً أو رميه.
لا تستعمل الدواء إذا بدا المحلول بلون غير سليم، عكر أو يحوي جزيئات أو كتل ظاهرة للعين.
لا يجوز تخزين أدوية مختلفة بنفس العلبة.
بعد الإستعمال أدخل القلم/المحقنة إلى وعاء مقاوم للوخز.
إسأل الطبيب، الصيدلي أو الممرضة عن كيفية التخلص من الوعاء. لا تعاود إستعمال الوعاء.
لا يجوز رمي الأدوية إلى القمامة البيتية أو داخل المجاري البيتية. إسأل الصيدلي الخاص بك عن كيفية التخلص من أدوية لم تعد بحاجتها بعد.
هذه الوسائل تساعد في الحفاظ على البيئة.

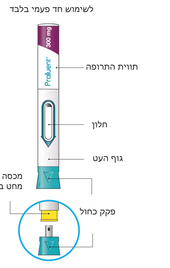
6) معلومات إضافية
بالإضافة للمادة الفعالة، يحتوي كل قلم/محقنة أيضاً على المواد غير الفعالة التالية:
Sucrose, L-Histidine/L-Histidine monohydrochloride monohydrate, Polysorbate 20, Water for injection.

كيف يبدو الدواء وما هو محتوى العلبة:
پرالوئنت هو محلول للحقن، رائق، عديم اللون إلى أصفر فاتح اللون، ضمن قلم/محقنة جاهزة للإستعمال.
پرالوئنت 75 ملغ/ملل: كل قلم جاهز للإستعمال ذو الزر الأخضر/محقنة جاهزة للإستعمال ذات مكبس أخضر تحتوي على 1 ملل محلول، وتحرر مقداراً دوائياً واحداً قدره 75 ملغ أليروكوماب.
تتوفر علب ذات 1، 2 أو 6 أقلام/محاقن، لا تسوّق كافة أحجام العلب.
پرالوئنت 150 ملغ/ملل: يتوفر بحجمين - 1 ملل، 2 ملل.
<u>1 ملل</u>:
كل قلم جاهز للإستعمال ذو الزر الرمادي/محقنة جاهزة للإستعمال ذات مكبس رمادي تحتوي على 1 ملل محلول، وتحرر مقداراً دوائياً واحداً قدره 150 ملغ أليروكوماب.
تتوفر علب ذات 1، 2 أو 6 أقلام/محاقن، لا تسوّق كافة أحجام العلب.
<u>2 ملل</u>:
كل قلم جاهز للإستعمال بدون زر يحتوي على 2 ملل محلول، ويحرر مقداراً دوائياً واحداً ذو 300 ملغ أليروكوماب.
تتوفر علب ذات 1 أو 3 أقلام، لا تسوّق كافة أحجام العلب.
هذه النشرة لا تحتوي على كافة المعلومات عن المستحضرات. إذا توفر لديك أي سؤال أو إذا لم تكن واثقاً من أمر ما، الرجاء مراجعة الطبيب.
إسم صاحب الإمتياز، المستورد وعنوانه: سانوفي - أڤنتيس إسرائيل م.ض.، شارع بني - چاؤون 10، نتانيا.
رقم سجل الدواء في سجل الأدوية الحكومي في وزارة الصحة:
پرالوئنت 75 ملغ/ملل: 156-08-34583
پرالوئنت 150 ملغ/ملل: 156-09-34568
من أجل سهولة وتهوين القراءة، تمت صياغة هذه النشرة بصيغة المذكر. على الرغم من ذلك، فإن الدواء مخصص لكلا الجنسين.
تم إعدادها في أيار 2023 بموجب تعليمات وزارة الصحة.

Technische Information / Technical information

SAP-Nr. / Plant PM code:	892044	Kontur / Outline	
Datum / Date:	12.07.2023 AR04		
Version:	S1	Druckbare Farben / printing Colours:	
DMC-Inhalt / DMC content:	<MAT>892044	Black	
Abmessungen / Dimensions:	420 × 948 mm		
Seite / Page:	1/2		

הוראות שימוש
פראלואנט 300 מ״ג/2 מ״ל תמיסה להזרקה בעט מוכן לשימוש
החלקים של עט הפראלואנט מתוארים בתמונה זו.



מידע חשוב
* שמור את עט הפראלואנט מחוץ להישג ידם ושדה ראייתם של ילדים.
* קרא בעיון את כל ההוראות לפני השימוש בפראלואנט.
* נהג לפי ההוראות בכל פעם שאתה משתמש בעט פראלואנט.

אל תעשה:
* ✗ אל תיגע במכסה הבטיחות הצהוב.
* ✗ אל תשתמש בעט אם הוא נפל או נפגע.
* ✗ אל תשתמש בעט אם הפקק הכחול חסר או לא מחובר בצורה בטוחה.
* ✗ אל תעשה שימוש חוזר בעט.
* ✗ אל תנער את העט.
* ✗ אל תקפיא את העט.
* ✗ אל תחשוף את העט לחום קיצוני.
* ✗ אל תחשוף את העט לאור שמש ישיר.

שמור על עלון זה. אם יש לך שאלה פנה לרופא, לרוקח או לאחות.

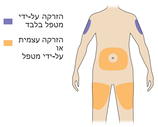
שלב א: הכנה להזרקה
לפני שתתחיל הכן לעצמך:
* עט הפראלואנט
* מדי אלכוהול
* כדור צמר גפן או גזה
* מכל עמיד לדקירות (ראה שלב ב׳ 7).

1. התכול על התווית על העט
* ודא שאתה מחזיק את התכשיר הנכון ובמינון הנכון.
* בדוק את תאריך התפוגה: אם התאריך עבר אל תשתמש בתכשיר.
* אל תשתמש בעט פראלואנט אם נפל על משטח קשיח או נפגם.

2. בדוק את החלון
* ודא שהתוכל צלול, ללא צבע או בצבע צהוב בהיר ונקי מחלקיקים - אם לא, אל תשתמש (ראה איור A).
* אל תשתמש בתרופה אם התמיסה דהויה או עכורה, או אם היא מכילה פתיתים או חלקיקים נראים לעין.
* ייתכן תרחיה בועת אוויר, זה תקין.
* אל תשתמש אם הצבע בחלון הינו צהוב חזק (ראה איור B).

3. אפשר לעט להתחמם בטמפרטורת החדר במשך 45 דקות.
* זה חשוב כדי לאפשר מתן של כל המנה ועוזר להקטין תוסר נוחות.
* אל תחמם את העט, חן לו להתחמם לבד.
* אל תחזיר את העט למקרר.

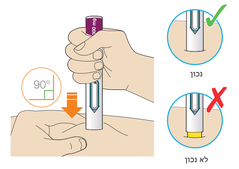
4. הכן את מקום ההזרקה
* שטוף את הידיים עם מים וסבון ויבש אותן עם מגבת.
* אתה יכול להזריק ב:
  - חלק העליון של הירך
  - בטן (למעט האזור של 5 ס״מ מסביב לטבור)
  - חלק חיצוני של זרוע עליונה (במתן על-ידי המטפל שלך בלבד)
* אתה יכול להזריק לעצמך בעזרת בישיבה או בעמידה.
* נקה את העור באזור ההזרקה עם פד אלכוהול.
* אל תזריק בעור רגיש, קשה, אדום או חם.
* אל תזריק בשום אזור בו יש וריד נראה לעין.
* הזרק כל פעם במקודה שונה.
* אל תזריק פראלואנט באותה נקודה עם תרופות מזרקות אחרות.



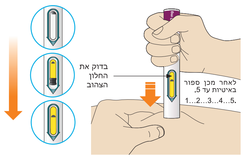
שלב ב: כיצד להזריק
1. לאחר השלמת כל השלבים של "שלב א: הכנה להזרקה", הסר את הפקק הכחול
* אל תסיר את הפקק הכחול לפני שאתה מוכן להזרקה.
* אל תחזיר את הפקק הכחול למקומו.
* אל תשתמש בעט אם הפקק הכחול חסר או שאינו מחובר היטב.

2. החזק את עט הפראלואנט בצורה כזו.
* אל תיגע במכסה הבטיחות הצהוב.
* ודא שאתה יכול לראות את החלון.
* אל תצמיד את העט לעורך עד שתהיה מוכן להזריק.

3. הצמד את מכסה הבטיחות הצהוב לעורך בזווית של בערך 90°.
* צבוט את העור כדי לוודא כי מקום ההזרקה הוא יציב.
* לחץ והחזק את העט צמוד לגופך עד שמכסה הבטיחות הצהוב נדחף עד הסוף לתוך העט והחזק (ראה איור).
* העט לא יעבוד אם מכסה הבטיחות הצהוב לא נלחץ עד הסוף.
* יהיה קליק כשתתחיל ההזרקה. החלון יתחיל לשנות את צבעו לצהוב.

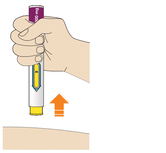


4. המשך להחזיק את העט צמוד לעורך.
* ייתכן שתשמע קליק שני.
* בדוק שכל החלון שינה את צבעו לצהוב.
* לאחר מכן, החל לספור עד 5 באיטיות.



5. ודא שהחלון שינה את הצבע לצהוב, הסר שאתה מזיז את העט.
* אם החלון לא שינה לחלוטין את צבעו לצהוב, הסר את העט ופנה לרופא, רוקח או אחות.
* אל תזריק לעצמך מנה שנייה מבלי לדבר עם הרופא, הרוקח או האחות.

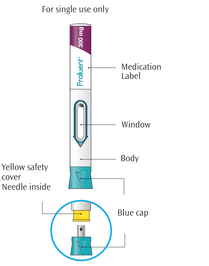
6. הרחק את העט מעורך.
* אל תשפשף את העור לאחר ההזרקה
* אם אתה רואה דם, הצמד כדור צמר גפן או גזה למקום ההזרקה עד שהדימום נפסק.



7. השלך את העט והפקק.
* אל תחזיר את הפקק הכחול למקומו.
* השלך את העט ואת הפקק הכחול למכל לאיסוף מחטים ועטים משומשים (עמיד לניקורות) מיד לאחר ההזרקה.
* שאל את הרופא, הרוקח או האחות כיצד להשליך את המכל.
* שמור תמיד את המכל מחוץ להישג ידם וטווח ראייתם של ילדים.

892044/A804

INSTRUCTIONS FOR USE
Praluent 300 mg/2 ml solution for injection in a pre-filled pen
The parts of the Praluent pen are shown in this picture.



Important information
* The medicine is injected under your skin and can be given by yourself or by someone else (a caregiver).
* It is important that you do not try to give yourself or someone else the injection unless you have received training from your 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 reach and sight of children.
✓ Read all of the instructions carefully before using the Praluent pen.
✓ Follow the instructions every time you use a Praluent pen.

Do not:
✗ Do not touch the yellow safety cover.
✗ Do not use the pen if it has been dropped or damaged.
✗ Do not use the pen if the blue cap is missing or not securely attached.
✗ Do not re-use a pen.
✗ Do not shake the pen.
✗ Do not freeze the pen.
✗ Do not expose the pen to extreme heat.
✗ Do not expose the pen to direct sunlight.

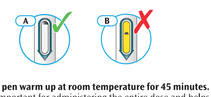
Keep this leaflet. If you have a question, refer to a doctor, pharmacist or nurse.

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, 7).

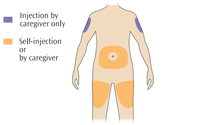
1. Look at the label on the pen
* Check that you have the correct product and the correct dose.
* Check the expiry date: do not use if this date has passed.
* Do not use the Praluent pen if it has been dropped on a hard surface or damaged.

2. Look at the window
* Check that the liquid is clear, colorless or pale yellow and free of particles – if not, do not use (see picture A).
* Do not use this medicine if the solution is discolored or cloudy, or if it contains visible flakes or particles.
* You may see an air bubble. This is normal.
* Do not use if the window is solid yellow (see picture B).



3. Let the pen warm up at room temperature for 45 minutes.
* This is important for administering the entire dose and helps minimize discomfort.
* Do not heat the pen, let it warm up on its own.
* Do not put the pen back in the refrigerator.

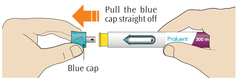
4. Prepare the injection site
* Wash your hands with soap and water and dry with a towel.
* You can inject into:
  - the top of your thighs
  - belly (except for the 5 cm area around the navel)
  - outer side of the upper arm (to be given by your caregiver only).
* You can stand or sit to give yourself an injection.
* Clean the skin in the injection area with an alcohol wipe.
* Do not inject into skin that is tender, hard, red or hot.
* Do not inject into an 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.



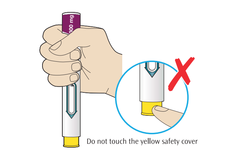
892044/A804

STEP B: HOW TO INJECT

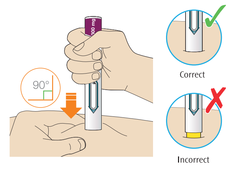
1. After completing all steps in "Step A: Getting ready for an injection", pull off the blue cap
* Do not pull off the blue cap until you are ready to inject.
* Do not put the blue cap back on.
* Do not use the pen if the blue cap is missing or not securely attached.



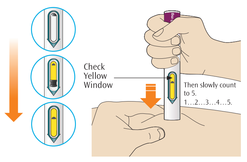
2. Hold the Praluent pen like this.
* Do not touch the yellow safety cover.
* Make sure you can see the window.
* Do not press the pen down against your skin until you are ready to inject.



3. Press the yellow safety cover onto your skin at roughly a 90° angle.
* Pinch the skin to be sure that the injection site is firm.
* Press and firmly hold the pen against your body until the yellow safety cover is pushed all the way into the pen and hold (see picture)
* The pen will not work if the yellow safety cover is not depressed fully.
* There will be a click when the injection starts. The window will start to turn yellow.

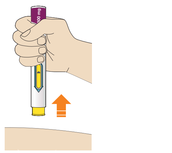


4. Keep holding the pen against your skin.
* You may hear a second click.
* Check that the entire window has turned yellow.
* Then, slowly count to 5.

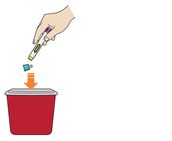


5. Check that the window has turned yellow, before removing the pen.
* If the window has not turned completely yellow, remove the pen and refer to the doctor, pharmacist or nurse.
* Do not give yourself a second injection without speaking to your doctor, pharmacist or nurse.

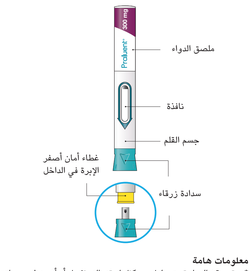
6. Pull the pen away from your skin.
* Do not rub the skin after the injection
* If you see any blood, press a cotton ball or gauze on the injection site until the bleeding stops.



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



تعليمات الإستعمال
پرالوِنت 300 ملغ/2 ملل محلول للحقن بقلم جاهز للإستعمال
أجزاء قلم پرالوِنت موصوفة في هذه الصورة.



معلومات هامة
* يتم حقن الدواء تحت جلدك ويمكنك إستعماله بنفسك أو أن يعطي بمساعدة شخص آخر (معالج).
* من المهم ألا تحاول الحقن لنفسك أو لشخص آخر بدون تلقي إرشاد من المعالج الخاص بك.
* بالإمكان إستعمال هذا القلم لمرة واحدة فقط، ويجب رميه بعد الإستعمال.

إفعل:
✓ إحفظ قلم پرالوِنت بعيداً عن متناول أيدي ومجال رؤية الأطفال.
✓ إقرأ بتمعن كافة التعليمات قبل إستعمال پرالوِنت.
✓ تصرف وفقا للتعليمات في كل مرة تستعمل فيها قلم پرالوِنت.

لا تفعل:
✗ لا تلمس غطاء الأمان الأصفر.
✗ لا تستعمل القلم إذا سقط أو تضرر.
✗ لا تستعمل القلم إذا كانت السدادة الزرقاء ناقصة أو غير موصولة بشكل آمن.
✗ لا تعاود إستعمال القلم.
✗ لا تخض القلم.
✗ لا يجوز تجميد القلم.
✗ لا تُعرِّض القلم لحرارة شديدة.
✗ لا تُعرِّض القلم لضوء الشمس المباشر.

إحتفظ هذه النشرة. إذا توفر لديك أي سؤال راجع الطبيب، الصيدلي أو المرضة.

المرحلة أ: تحضير للحقن
قبل أن تبدأ جهز لنفسك:
* قلم پرالوِنت
* مسحات كحولية
* كرة من القطن أو شاش
* وعاء مقاوم للوخز (أنظر المرحلة ب 7).

892044/A804

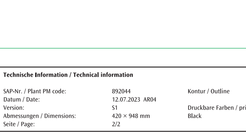
المرحلة ب: كيفية الحقن

1) بعد إتمام كل المراحل الخاصة بـ «مرحلة أ: تحضير للحقن»، قم بنزع السدادة الزرقاء
* لا تنزع السدادة الزرقاء قبل أن تكون مستعداً للحقن.
* لا تعيد السدادة الزرقاء إلى مكانها.
* لاتستعمل القلم إذا كانت السدادة الزرقاء ناقصة أو غير موصولة جيداً.

2) أمسك قلم پرالوِنت بهذه الطريقة.
* لا تلمس غطاء الأمان الأصفر.
* تأكد من أنك تستطيع رؤية النافذة.
* لا تلتصق القلم بجلدك حتى تكون مستعداً للحقن.

3) أضغط غطاء الأمان الأصفر إلى جلدك بزاوية قدرها 90 درجة تقريباً.
* أقرص الجلد للتأكد من ثبات مكان الحقن.
* إضغط وأمسك القلم ملاصقا لجسمك إلى أن يتم دفع غطاء الأمان الأصفر حتى النهاية داخل القلم وواصل الإمساك (أنظر الرسم)
* لن يعمل القلم إذا لم يتم ضغط غطاء الأمان الأصفر حتى النهاية.
* سنسمع صوت طقة عند بدء الحقن. سيبدأ لون النافذة بالتغير إلى اللون الأصفر.

4) واصل إمساك القلم بشكل ملاصق لجلدك.
* من الجائز أن تسمع صوت طقة ثانية.
* تأكد من تغير لون كامل النافذة إلى الأصفر.
* من ثم، إبدأ العد حتى 5 ببطء.



5) قبل تحريك القلم، تأكد من تغير لون النافذة إلى الأصفر.
* إذا لم يتغير لون النافذة بشكل تام إلى اللون الأصفر، قم بنزع القلم وتوجه إلى الطبيب، الصيدلي أو المرضة.
* لا تحقن لنفسك مقداراً دوائياً ثانياً من دون التحدث مع الطبيب، الصيدلي أو المرضة.

6) قم بإبعاد القلم عن جلدك.
* لا تفرك الجلد بعد الحقن.
* إذا لاحظت وجود دم، قم بالضغط كرة من القطن أو الشاش لمكان الحقن إلى أن يتوقف النزف.

7) إرم القلم والسدادة.
* لا تعد السدادة الزرقاء إلى مكانها.
* إرم القلم والسدادة الزرقاء إلى وعاء تجميع الإبر والأقلام المستعملة (مقاوم للوخز) حالا بعد الحقن.
* إسأل الطبيب، الصيدلي أو المرضة حول كيفية التخلص من الوعاء.
* إحفظ دائما الوعاء بعيداً عن متناول أيدي ومجال رؤية الأطفال.

892044/A804

1) أنظر إلى الملصقة الموجودة على القلم
* تأكد من أنك تمسك المستحضر الصحيح والمقدار الدوائي الصحيح.
* تحقق من تاريخ إنقضاء الصلاحية: إذا إنقضى التاريخ فلا تستعمل المستحضر.
* لا تستعمل قلم پرالوِنت إذا سقط على سطح صلب أو تضرر.

2) إفحص النافذة
* تأكد من أن السائل رائق، عديم اللون أو بلون أصفر فاتح وخال من الجزيئات – إذا لم يكن كذلك، فلا تستعمله (أنظر الرسم A).
* لا تستعمل الدواء إذا كان المحلول باهتاً أو عكراً، أو إذا إحتوى على فتات أو جسيمات ظاهرة للعين.
* من الجائز أن ترى فقاعة هواء، هذا الأمر سليم.
* لا تستعمل إذا كان اللون في النافذة هو أصفر شديد الصفرة (أنظر الرسم B).

3) دع القلم ليدفئ بدرجة حرارة الغرفة لمدة 45 دقيقة.
* هذا مهم لإتاحة إعطاء كامل المقدار الدوائي والمساعدة على تقليل عدم الراحة.
* لا تدفئ القلم، دعه ليدفئ من تلقاء نفسه.
* لا تعيد القلم إلى البراد.

4) حضر مكان الحقن.
* إغسل يدك بالماء والصابون وجففهما بواسطة منشفة.
* يمكن الحقن في:
  - الجزء العلوي من الفخذ
  - البطن (عدا المنطقة 5 سم من حول السرة)
  - الجزء الخارجي من أعلى الذراع (بالإعطاء من قبل المعالج الخاص بك فقط)
* بإمكانك الحقن لنفسك بينما تكون جالساً أو واقفاً.
* نظف الجلد في منطقة الحقن بواسطة ضماد كحولي.
* لا تحقن في جلد حساس، صلب، أحمر أو ساخن.
* لا تحقن في أي منطقة يبدو فيها ورید ظاهر للعين.
* لحقن كل مرة في نقطة مختلفة.
* لا تحقن پرالوِنت في نفس النقطة مع أدوية أخرى تعطى بالحقن.

Technische Information / Technical information

SAP-Nr. / Plant PM code:	892044	Kontur / Outline	
Datum / Date:	12.07.2023 A804		
Version:	51	Druckbare Farben / printing Colours:	
Abmessungen / Dimensions:	420 × 948 mm	Black	
Seite / Page:	2/2		

15/01/2024 15:41 - VISTAlink folder 4263425 - Page 2/4