מרץ 2020

רופא/ה רוקח/ת נכבד/ה,

בעקבות עדכון התוויית התכשיר, חברת סאנופי-אוונטיס ישראל בע"מ מבקשת להודיע על עדכון העלון לצרכן והעלון לרופא של התכשיר:

PRALUENT 75 MG ; PRALUENT 150 MG, *solution for S.C. injection.*

החומר פעיל:

Alirocumab

ההתוויה העדכנית:

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.

בעקבות כך הסעיפים בהם נעשו העדכונים העיקריים בעלונים:

<u>בעלון לצרכן:</u>

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

סאנופי אוונטיס ישראל, רח' בני גאון 10, פארק פולג, ת.ד. 8090, נתניה דרום 42504
טל': 09-8633700 פקס: 09-8851444

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.

בעלון לרופא:

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.

5.PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clinical efficacy and safety in primary hypercholesterolaemia and mixed dyslipidaemia

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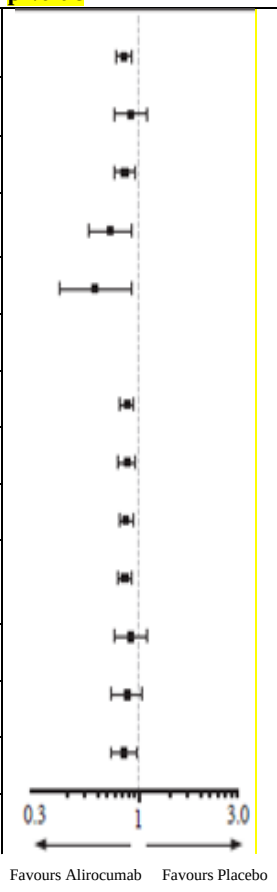
Clinical efficacy and safety in prevention of cardiovascular events

ODYSSEY OUTCOMES study
A multicentre, double-blind, placebo-controlled trial included 18,924 adult patients (9462 alirocumab; 9462 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/dL), 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 2615 (27.7%) of 9451 patients treated with alirocumab required dose adjustment to 150 mg Q2W. Of these 2615 patients, 805 (30.8%) were down-titrated to 75 mg Q2W. Overall, 730 (7.7%) of 9451 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=9462 n (%)	Placebo N=9462 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[f]
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.

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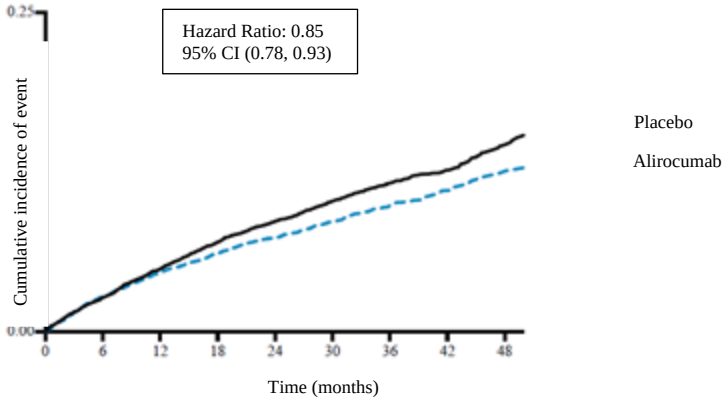
Figure 1 Primary Composite Endpoint Cumulative Incidence Over 4 Years in ODYSSEY OUTCOMES

Overall Population



Paediatric population

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

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

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות . בנוסף ניתן לקבלם מודפסים על ידי פנייה לבעל הרישום, סאנופי-אוונטיס ישראל בע"מ, רח' בני גאון 10 נתניה או בטלפון : 09-8633700 .להלן הקישור לאתר משרד הבריאות :
https://www.old.health.gov.il/units/pharmacy/trufot/index.asp?safa=h

בברכה,

סאנופי-אוונטיס ישראל בע"מ

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