Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Alirocumab (rch)

Proprietary Product Name: Praluent

Sponsor: Sanofi-Aventis Australia Pty Ltd

December 2019

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ACPM	Advisory Committee on Prescription Medicines
ACS	Acute coronary syndrome
ADA	Anti-drug antibody
AE	Adverse event
AIHW	Australian Institute of Health and Welfare
ALT	Alanine aminotransferase
Apo B	Apolipoprotein B
ARTG	Australian Register of Therapeutic Goods
BMI	Body mass index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CPK	Creatinine phosphokinase
CV	Cardiovascular
CVD	Cardiovascular disease
DILI	Drug-induced liver injury
eGFR	Estimated glomerular filtration rate
HDL-C	High density lipoprotein cholesterol
heFH	Heterozygous familial hypercholesterolaemia
HR	Hazard ratio
IgG1	Immunoglobulin G1
ITT	Intention to treat

Abbreviation	Meaning
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
LDLR	Low density lipoprotein receptor
LFT	Liver function test
LMT	Lipid-modifying therapy
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
non-FH	Non-familial hypercholesterolaemia
non-HDL-C	Non-high density lipoprotein cholesterol
NSTEMI	Non-ST segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
PCSK9	Pro-protein convertase subtilisin kexin type 9
PSUR	Periodic safety update report
PT	Preferred Term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RMP	Risk management plan
SAE	Serious adverse event
SC	Subcutaneous(ly)
SOC	System Organ Class
STEMI	ST segment elevation myocardial infarction
TEAE	Treatment emergent adverse event
TG	Triglycerides
UA	Unstable angina
ULN	Upper limit of normal
α	Alpha

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	29 October 2019
Date of entry onto ARTG:	1 November 2019
ARTG numbers:	238285, 238299, 238304, 238305
, *Black Triangle Scheme*	No
Active ingredient:	Alirocumab (rch)
Product name:	Praluent
Sponsor's name and address:	Sanofi-Aventis Australia Pty Ltd Locked Bag 2227 North Ryde BC, NSW, 1670
Dose forms:	Solution for injection
Strengths:	75 mg/mL and 150 mg/mL
Containers:	Prefilled syringe and prefilled pen
Pack sizes:	1 (starter pack), 1, 2, 6
Approved therapeutic use:	***Primary hypercholesterolaemia*** *Praluent is indicated as an adjunct to diet and exercise to reduce LDL-C in adults with primary (heterozygous familial or non-familial) hypercholesterolaemia in patients with moderate to very high cardiovascular risk:* • *In combination with a statin, or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with maximum tolerated dose of a statin,* • *Alone or in combination with other lipid lowering therapies in patients who are statin intolerant or for whom a statin is contraindicated who are unable to reach LDL-C goals.* ***Prevention of cardiovascular events*** *Praluent is indicated to reduce the risk of cardiovascular events (myocardial infarction, stroke, unstable angina requiring hospitalisation) in adults with established cardiovascular disease, in combination with optimally dosed statins and/or other lipid-lowering therapies (see section 5.1 Pharmacodynamic properties, CLINICAL TRIALS).*

Route of administration:	Subcutaneous
Dosage:	The recommended starting dose of Praluent is 75 mg once every 2 weeks or 300 mg once every 4 weeks (monthly), administered subcutaneously. For further information see the Product Information.

Product background

This AusPAR describes the application by Sanofi-Aventis Australia Pty Ltd (the sponsor) to register Praluent (alirocumab (rch)) solution for injection for the following proposed extension of indications:

> ***Primary hypercholesterolaemia and mixed dyslipidaemia***
>
> *Praluent is indicated as an adjunct to diet and exercise to reduce LDL-C in adults with heterozygous familial or non-familial hypercholesterolaemia, or mixed dyslipidaemia:*
>
> - *In combination with a statin, or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with 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 who are unable to reach LDL-C goals.*
>
> ***Prevention of cardiovascular events***
>
> *Praluent is indicated:*
>
> - *To reduce the risk of major adverse cardiovascular events (coronary heart disease death, myocardial infarction, stroke, unstable angina requiring hospitalisation) in adults with established cardiovascular disease;*
> - *To reduce the risk of all-cause mortality in adults with established cardiovascular disease;*
> - *To reduce the risk of coronary heart disease death and cardiovascular mortality in adults with established cardiovascular disease with LDL-C > 100 mg/dL (2.59 mmol/L).*

In 2009, about one third of deaths in Australia were the result of cardiovascular disease (CVD); and 2,027 per 100,000 people were hospitalised with CVD as a principal diagnosis in the period from 2009 to 2010.[1] Epidemiological and intervention studies have demonstrated a strong, linear relationship between low-density lipoprotein cholesterol (LDL-C) levels and cardiovascular (CV) events.[2,3,4,5,6] Although a number of therapeutic options are registered for use in patients with hypercholesterolaemia, they do not

[1] Australian Institute of Health and Welfare.
[2] LaRosa, J.C. et al. (2005), Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*, 2005; 352: 1425-1435.
[3] Cannon, C.P. et al. (2004), Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*, 2004; 350: 1495-1504.
[4] Ridker, P.M. et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*, 2008; 359: 2195-27.
[5] Grundy, S.M. et al. (2004), Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*, 2004; 110: 227-239.
[6] European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the management of dyslipidaemias. *Eur Heart J*, 2011; 32: 1769-1818.

universally result in the achievement of target serum lipid levels and have adverse effects in the population for which they are suitable. A reduction in serum lipids as measured by LDL-C has been associated with a reduction in the risk of CV events and serum lipid reduction is advocated in international guidelines for managing CV risk.

Alirocumab is a recombinant human immunoglobulin G1 (IgG1) isotype monoclonal antibody that specifically binds to pro-protein convertase subtilisin/kexin type 9 (PCSK9) and inhibits circulating PCSK9 from binding to the LDL receptor (LDLR) on the surface of the hepatocyte. By binding to PCSK9, it increases the concentration of LDLR on hepatic cells by inhibiting LDLR degradation and promoting recycling of the receptor. The inhibition also increases LDLR expression. It differs from statins in its mode of action although the action of statins leads to an increase in LDLR on the hepatocyte cell surface by increasing LDLR expression. The alirocumab-PCSK9 complex is internalised in the hepatocyte and degraded in lysosomes, thereby removing PCSK9 from circulation.

At the time of this submission alirocumab was approved in patients with heterozygous familial hypercholesterolaemia (heFH) and patients with clinical atherosclerotic CVD or high or very high CV risk in patients with hypercholesterolaemia with statins, with statin and other lipid lowering therapies or without statins but with other lipid lowering therapies in statin intolerant patients.

This submission sought to remove the restriction to patients with clinical atherosclerotic CVD, or hypercholesterolaemia with high or very high CV risk and extend the existing indication for hyperlipidaemia to include patients with non-familial hypercholesterolaemia and mixed dyslipidaemia. The submission also sought the use of alirocumab as monotherapy for this indication.

In addition, the submission also sought to add an indication for cardiovascular prevention, supported by the ODYSSEY OUTCOMES trial. It was proposed that alirocumab may be used as monotherapy or in addition to statins or other lipid lowering therapies.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 17 May 2016 for the following indications:

> *Praluent/Golyra/Eliriduc is indicated as an adjunct to diet and exercise in adults with heterozygous familial hypercholesterolaemia or clinical atherosclerotic cardiovascular disease:*
>
> - *In combination with a statin, or statin with other lipid-lowering therapies or,*
> - *In combination with other lipid-lowering therapies in patients who are statin-intolerant.*
>
> *The effect of Praluent/Golyra/Eliriduc on cardiovascular morbidity and mortality has not yet been determined (see Clinical Trials).*

On 12 September 2017 the following extension of indications was approved:

> *Praluent is indicated as an adjunct to diet and exercise to reduce LDL-C in adults with one or more of: heterozygous familial hypercholesterolaemia, clinical atherosclerotic cardiovascular disease, or hypercholesterolemia with high or very high cardiovascular risk.*
>
> - *In combination with a statin, or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with maximum tolerated dose of a statin or,*

- *In combination with other lipid lowering therapies in patients who are statin intolerant or for whom a statin is contraindicated who are unable to reach LDL-C goals.*

The effect of Praluent on cardiovascular morbidity and mortality has not yet been determined (see Clinical Trials).

At the time the TGA considered this application, a similar application had been approved in the European Union (approved on 31 January 2019), United States of America (approved on 26 April 2019) was under consideration in Switzerland (submitted 25 July 2018), Singapore (submitted 1 August 2018) and Canada (submitted 30 August 2018).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 1 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2018-02973-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	31 August 2018
First round evaluation completed	31 January 2019
Sponsor provides responses on questions raised in first round evaluation	1 April 2019
Second round evaluation completed	15 May 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	30 June 2019
Sponsor's pre-Advisory Committee response	16 July 2019
Advisory Committee meeting	1-2 August 2019 and 4 October 2019[7]
Registration decision (Outcome)	29 October 2019
Completion of administrative activities and registration on ARTG	1 November 2019
Number of working days from submission dossier acceptance to registration decision*	209

*Statutory timeframe for standard applications is 255 working days

[7] Advice on this submission was sought at two separate Advisory Committee meetings.

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator has not recommended approval of the expansion of the population for hyperlipidaemia to include patients with non-familial hypercholesterolaemia and mixed dyslipidaemia. The evaluator recommended approval of an indication for the prevention of CV events. The evaluator has not recommended approval of monotherapy for either of the indications.

The clinical dossier comprised:

- 1 Phase IIIb study; Study EFC11570 (published as the ODYSSEY OUTCOMES trial);
- a Clinical Overview, Summary of Clinical Efficacy and Summary of Clinical Safety with Appendix; and
- literature references.

Pharmacology

No new pharmacology studies were provided in the submission.

Efficacy

Prevention of cardiovascular events

The ODYSSEY OUTCOMES trial was a single Phase IIIb, multicentre, multinational, randomised, double blind, placebo controlled, parallel group study conducted between October 2012 and January 2018. It included 18,924 patients who had been hospitalised for an acute coronary syndrome (ACS) event (that is, an ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI) or high risk unstable angina (UA), 4 to 52 weeks previously) and who had inadequately controlled lipid levels despite evidence based lipid lowering therapy (intensive atorvastatin/rosuvastatin therapy or maximally tolerated dose or either of these statins or other non-statin lipid modifying therapy (LMTs; optimised statin therapy)). Inadequate lipid control was defined as LDL-C ≥ 1.81 mmol/L, or apolipoprotein B (Apo B) ≥0.8 mmol/L, or non-HDL-C ≥ 2.59 mmol/L. All qualifying lipid levels were measured after a minimum 2 weeks of optimised statin therapy. Exclusion criteria were numerous including age ≤ 40 years, triglycerides (TG) > 4.52 mmol/L, use of fibrates other than fenofibrate, a new ACS event within 2 weeks of randomisation, coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) planned or performed within 2 weeks of randomisation, unstable LMT dosing for at least 2 weeks, and any increased dose of LMT after the commencement of the run-in period without requalification based on

lipids, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, transaminases > 3 x upper limit of normal (ULN) or hepatitis B or C.

The study comprised three periods. A run in period of 2 to 16 weeks, in which background LMT was adjusted to ascertain the patient was receiving intensive statin treatment (atorvastatin 40 or 80 mg or rosuvastatin 20mg or 40 mg) or the maximally tolerated doses of these given statins or other non-statin LMTs prior to randomisation, and to stabilise this treatment. The second was a double-blind, randomised (alirocumab 75 mg subcutaneously (SC) every 2 weeks (Q2W) or placebo), treatment period during which the background LMT could not be modified except for safety reasons, then 8 weeks follow up after the final study visit at Month 64. The median follow up was 33 months.

The study screened 35,437, randomised 18,924 to (9462 to each study treatment) in addition to background LMT. Over 99% received their allocated study treatment. Randomisation was stratified according to country.

Most patients were white (79.4%), male (74.8%) with a mean age of 58.6 years. Around 26.9% were aged ≥ 65 years. The mean body mass index (BMI) was 28.49 kg/m^2 and 33.3% had a BMI ≥ 30 kg/m^2. Around 34% of patients had a history of coronary heart disease (CHD) before the index ACS event (21.4% had angina and 19.2% had a myocardial infarction (MI)). Overall, 88.9% of patients had at least one significant cardiovascular risk factor, including dyslipidaemia (66.7%), hypertension (64.7%), family history of coronary artery disease (CAD; 35.8%), and type II diabetes mellitus (24.4%). Other CVD included congestive cardiac failure (CHF; 14.9%), cerebrovascular disease (5.0%), and peripheral arterial disease (4.0%). Only 25.4% of patients had normal renal function, 61.2% had mild renal impairment (eGFR ≥ 60 to < 90 mL/min), 3.1% had moderately decreased renal function and 0.3% had severe renal impairment. Index events were MI 83.2% (34.6% STEMI, 48.6% NSTEMI) and unstable angina (16.8%). Approximately 72% had revascularisation for their index event.

At Baseline, 86.4% of patients had at least one lipid criterion not adequately controlled (LDL-C 80.2%, Apo B 49.5%, or non-HDL-C 74.4%). A total of 38.3% of patients had baseline TGs ≥ 1.7 mmol/L.

Approximately 8% of patients did not qualify with LDL-C criterion but did qualify based on Apo B (0.3%) and/or non-HDL-C (7.2%) criteria, and 0.5% of randomised patients had adequately controlled lipid abnormalities (major protocol deviations). At randomisation, most patients (88.8%) were receiving intensive statin therapy, and 8.5% were receiving low or moderate dose statin (most commonly for muscle symptoms and/or increased creatinine phosphokinase (CPK). Only 7.5% of patients were taking LMT other than statins.

Alirocumab dosing commenced at 75 mg SC Q2W. After 2 months the dose of alirocumab was adjusted to target a range of LDL-C of 0.6 to 1.29 mmol/L; 75 mg Q2W if the LDL-C was < 1.29 mmol/L, or 150 mg SC Q2W if the LDL-C was ≥ 1.29 mmol/L. Further adjustment by down-titration from 150 mg SC Q2W to 75 mg SC Q2W or from 75mg SC Q2W to placebo was according to LDL-C values (2 consistent consecutive values were < 0.6 mmol/L). Background LMT was continued. About 27.7%% were up-titrated and of those about 30.8% (8.5% of the total alirocumab group) were down titrated to 75 mg Q2W.

The protocol was amended in December 2013 to allow patients with a time from index event to randomisation to extend from 16 weeks to 52 weeks. The definition of the endpoints changed in December 2013 to exclude silent MI, subdural haematomas in stroke, and restenosis of a PCI site and to define high risk UA as needing PCI/CABG or having ≥ 70% stenosis. Major protocol violations likely to impact the efficacy analysis occurred in 7.1% alirocumab versus 6.9% placebo. The most common reason was mean injection frequency (3.7% alirocumab versus 3.8% placebo), no LDL-C sample available at

the time of the potential up-titration (Visit 5 after 2 months of treatment; 1.6% alirocumab versus 0.9% placebo).

Overall 81% of the patients (78% alirocumab and 84% placebo) completed the double blind treatment period. Premature discontinuations of study treatment occurred in 21.9% alirocumab (n = 2073) and 15.8% placebo (n = 1496). The 730 patients who switched from alirocumab to placebo because of low LDL-C levels were considered discontinued. Deaths during follow up occurred in 3.5% versus 4.1% of alirocumab versus placebo patients, respectively. Discontinuation due to adverse events (AE) occurred in 3.8% alirocumab versus 3.7% placebo.

A final analysis was planned for after 1,613 patients experienced at least one primary endpoint event and for approximately 24 months after the date of the last randomised patient. Two interim analyses were planned: the first after 50% of primary endpoint events for futility and the second after 75% of events for futility and overwhelming efficacy. Control of Type I and Type II error were pre-specified. There were 11 protocol amendments during the course of the study, including readjustment of the sample size by 300 patients per treatment arm. A study of 9,300 patients per group (total 18,600) and 1,613 patients experiencing at least on primary endpoint event gave the study a 90% power (one-sided log-rank test at the overall 0.025 alpha (α) level) assuming a 15% risk reduction with the alirocumab treatment. The main analysis used the intention to treat (ITT) population.

Results of the primary efficacy endpoint:

- composite endpoint of CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, or UA requiring hospitalisation; alirocumab versus placebo: 9.5% versus 11.1% (hazard ratio (HR): 0.85; 95% confidence interval (CI): 0.78 to 0.93, p = 0.0003).

Results of the individual components of the primary efficacy endpoint:

- non-fatal MI; alirocumab versus placebo (HR: 0.86; 95% CI: 0.77 to 0.96, nominal p = 0.0058);
- fatal or non-fatal ischemic stroke; alirocumab versus placebo (HR: 0.73; 95% CI: 0.57 to 0.93, nominal p = 0.0097);
- risk of UA requiring hospitalisation; alirocumab versus placebo (HR: 0.61; 95% CI: 0.41 to 0.92, nominal p = 0.0177; and
- CHD death; alirocumab versus placebo (HR: 0.92; 95% CI: 0.76 to 1.11, p = 0.3824).

The main secondary endpoints:

- any CHD event (CHD death, non-fatal MI, UA requiring hospitalisation and ischemia-driven coronary revascularisation procedure, alirocumab versus placebo (HR: 0.88; 95% CI 0.81 to 0.95,p = 0.0013);
- any major CHD event (CHD death and non-fatal MI) alirocumab versus placebo (HR: 0.88; 95% CI 0.80 to 0.96, p = 0.0060);
- any CV event (non-fatal CHD event, any CV death, and non-fatal ischemic stroke), alirocumab versus placebo (HR: 0.87; 95% CI 0.81 to 0.94, p = 0.0003);
- composite event of all-cause mortality, non-fatal MI, and non-fatal ischemic stroke alirocumab versus placebo (HR: 0.86; 95% CI 0.79 to 0.93, p = 0.0003);
- CHD deaths alirocumab versus placebo (HR: 0.92; 95% CI: 0.76 to 1.11, p = 0.3824);
- CV deaths alirocumab versus placebo, for CV deaths (HR: 0.88; 95% CI: 0.74 to 1.05, nominal p = 0.1528);

- reduction in CHD and CV deaths were greater in alirocumab versus placebo patients with baseline LDL-C ≥ 2.59 mmol/L (major adverse cardiovascular events (MACE) 11.5% versus 14.9%; CHD death 2.5% versus 3.4%; ischaemic stroke 1.5% versus 2.4%; nonfatal MI 8.2% versus 10.3%; analysis by baseline characteristics not significant for the interaction) but there was no difference for other LDL-C categories, TIMI;[8] or REACH risk scores;[9] across the study
- All cause death alirocumab versus placebo (HR: 0.85; 95% CI: 0.73 to 0.98, nominal p=0.0261)

Lipid levels were tracked during the study and LDL-C lowering was consistent with that demonstrated in the registration submissions for alirocumab for the initial and current indications. In the on-treatment analysis of LDL-C after 4 months and 48 months of treatment the alirocumab group was 62.7% and 54.7% lower than placebo, respectively.

Safety

The safety information in the submission was derived from the ODYSSEY OUTCOMES trial. Patients who received at least one dose of alirocumab were included in the safety data (18,894: 9451 alirocumab, 9462 placebo). An overview of the AEs is shown in Table 2.

Table 2: ODYSSEY OUTCOMES trial; Overview of the adverse event profile, treatment-emergent adverse events; safety population

n(%)	Placebo (N=9443)	Alirocumab (N=9451)
Patients with any TEAE	7282 (77.1%)	7165 (75.8%)
Patients with any treatment emergent SAE	2350 (24.9%)	2202 (23.3%)
Patients with any TEAE leading to death	222 (2.4%)	181 (1.9%)
Patients with any TEAE leading to permanent treatment discontinuation	324 (3.4%)	343 (3.6%)
TEAE leading to alirocumab discontinuation	NA	339 (3.6%)
TEAE leading to placebo discontinuation[a]	324 (3.4%)	4 (<0.1%)

n(%) = number and percentage of patients with at least one TEAE
[a]For alirocumab group, it corresponds to patients who were were initially treated with alirocumab but then switched to placebo due to 2 consecutive LDL-C values <15 mg/dL and who subsequently discontinued treatment due to AE with onset after switching but during the TEAE period

TEAE = treatment emergent adverse event; SAE = serious adverse event; AE = adverse event; NA = not applicable; LDL-C = low density lipoprotein-cholesterol.

The most commonly reported AE by System Organ Class (SOC) in both groups were infections and infestations, and musculoskeletal and connective tissue disorders. The most common AE were nasopharyngitis, angina, hypertension, myalgia, and non-cardiac chest pain. The only AE by Preferred Term (PT) with an incidence of ≥ 2% in the alirocumab group and a ≥ 0.5% difference compared with placebo was injection site reaction. Injection site reactions were reported in 3.8% and 2.1% of the alirocumab and placebo groups, respectively and were more common in the few patients with neutralising anti-drug antibodies (ADA). Most patients who experienced injection sites had a single episode (alirocumab 70.8%; placebo 80.8%) and the majority were mild in severity (84.4% versus 90.1%).

Other serious adverse events (SAE) were reported in 23.3% and 24.9% of the alirocumab and placebo groups, respectively. The most common SAE in the alirocumab and placebo

[8] TIMI (Thrombolysis in Myocardial Infarction) Risk Score for Unstable Angina/Non–ST Elevation MI; the TIMI risk score is a simple prognostication scheme that categorises a patient's risk of death and ischemic events and provides a basis for therapeutic decision making.
[9] REACH (REduction of Atherothrombosis for Continued Health) Registry; A global registry of outpatients with established cardiovascular disease, analysed for risk factors and subsequent outcomes.

groups were non-cardiac chest pain (2.3% versus 2.4%), angina (1.2% versus 1.4%), pneumonia (1.0% versus 1.1%), and atrial fibrillation (0.9% versus 1.0%).

Discontinuations due to AEs occurred in 3.6% versus 3.4% of the alirocumab and placebo groups, respectively, most commonly myalgia (0.2% in each group), and injection site reactions (0.2% versus < 0.1%).

Hepatic events were similar between the two groups (2.2 events per 100 patient years), and the majority were mild or moderate. Of the 21 patients with potential drug-induced liver injury (DILI) events (15 alirocumab and 6 placebo group patients), events were considered to be related to statin therapy in 13 and 5 patients in the respective groups. In 5 of the alirocumab patients, potential DILI events were considered SAEs. Alirocumab was permanently discontinued and all patients recovered. One alirocumab receiving patient, met the criteria for Hy's law;[10] but it was attributed to concomitant treatment with benzylpenicillin and clarithromycin. The patient recovered and treatment with alirocumab was resumed without recurrence of liver function test (LFT) abnormalities.

The incidence of diabetes or 'diabetes complication' AEs was comparable in the alirocumab and placebo groups (8.7% versus 9.8%; (HR 0.92 (95% CI: 0.84, 1.01)). Similar proportions of patients had new onset diabetes during the treatment period in the alirocumab and placebo groups (9.6% versus 10.1%).

The incidence of general allergic AEs was comparable in the alirocumab and placebo groups (7.9% versus 7.8%); most commonly rash (1.2% versus 1.1%), pruritus (0.8% versus 0.7%), asthma (0.6% each), eczema (0.5% versus 0.6%), and conjunctivitis (0.4% versus 0.5%). Most events were mild to moderate in severity. Severe events were reported in 5.9% and 6.1% of the respective groups. SAEs were reported in 0.8% and 0.9% of the respective groups. General allergic SAEs with a fatal outcome were reported in eight patients in the alirocumab group and nine patients in the placebo group. Nearly all fatalities were due to respiratory failure due to non-allergic causes such as cardiac failure and pneumonia. One patient in the alirocumab group with a history of asthma died due to a sudden asthma crisis without trigger factors. The remaining patient in the placebo group choked on food. General allergic AEs leading to permanent discontinuation were reported in 0.4% of patients in each treatment group.

Pre-existing ADAs were present in 1.0% and 1.1% of the alirocumab and placebo groups, respectively. On-treatment ADAs developed in 5.5% versus 1.6%. Most ADAs were of low titre and transient. Neutralising ADAs were reported in 0.5% alirocumab (n = 43 out of 9091) and < 0.1% (6 out of 9097) of placebo patients. ADA responses, including neutralising antibodies did not appear to impact on LDL-C levels, and the numbers are too small to comment on the impact on the CV events.

The incidence of cataract was comparable in the alirocumab (1.3%) and placebo groups (1.4%).

The incidence of neurocognitive events was comparable between the alirocumab (1.5%) and placebo groups (1.8%). The most commonly reported neurocognitive AEs were memory impairment (0.4% versus 0.5%), and amnesia (0.3% in each group). Confusional state was reported more frequently in the alirocumab group (0.2%) compared with the placebo group (< 0.1%). However, an adjudicated alternative cause was identified for all but one patient in the alirocumab group.

A total of 0.1% and 0.2% of patients in the alirocumab and placebo groups, respectively, permanently discontinued study treatment due to a neurocognitive AE. Most events were mild or moderate in severity. Severe events were reported in 5.6% and 4.8% of patients in the respective groups. Neurocognitive SAEs were reported in 0.2% of patients in both

[10] Hy's Law: alanine aminotransferase > 3 x ULN and total bilirubin > 2 x ULN

treatment groups. One patient in the alirocumab group and three patients in the placebo group had neurocognitive events leading to death. The patient in the alirocumab group had metastatic colon cancer and respiratory failure.

There were no consistent differences in the rate of neurocognitive events between alirocumab-treated patients with two consecutive LDL-C < 25 mg/dL (0.65 mmol/L) and alirocumab treated patients without these low LDL-C levels.

The most recent periodic safety update report (PSUR) has been provided, covering the period of 24 September 2016 to 23 March 2017. During the reporting period, 358,248 alirocumab single units were sold worldwide, corresponding to approximately 14,927 patient-years for all alirocumab strengths. No safety actions were taken for safety reasons during the report period. No new safety signals were detected and no changes were made to the company core safety information for alirocumab. The sponsor proposes no change to the risk management plan (RMP) based on the cumulative post-marketing and clinical trial data

Risk management plan

The TGA has considered the European Union-risk management plan (EU-RMP; Version 4.2, dated 23 January 2019; data lock point 13 February 2018) with Australian Specific Annex (Version 3.1, dated 20 March 2019) and has no outstanding issues relating to the RMP.

Table 3 shows the provided summary of safety concerns and associated pharmacovigilance and risk minimisation strategies.[11]

Table 3: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Immunogenicity	ü	–	ü	–
	Systemic hypersensitivity reactions	ü	–	ü	–
Important potential risks	Neurocognitive disorders	ü	ü	ü	–
	Cataract (in context of very low LDL-C)	ü	–	ü	–
Missing information	Use in children and adolescents	ü	ü	ü	–
	Use in pregnant and lactating women	ü[1]	–	ü	–
	Use in patients with severe hepatic impairment	ü	–	ü	–

[11] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Long term use (> 5 years)	ü	ü	–	–
	Clinical impact of very low LDL-C (less than 25 mg/dL (0.65 mmol/L))	ü	ü	ü	–
	Influence of alirocumab on gonadal steroid hormones and gonadotropins (in men and women)	ü	ü	–	–

1) Routine risk minimisation for this safety concern includes the use of a specific pregnancy/drug exposure via parent data collection form and additional form on neonates/children that is attached to this form to document developmental defects up to six months after birth.

The sponsor has proposed seven new additional pharmacovigilance activities in this submission (Studies R727-CL-1532, R727-CL-1609, ALIROC07997, OBS14697, DFI14223, EFC14643 and EFC14660). These evaluator was satisfied these studies will address existing safety concerns. No additional risk minimisation activities are proposed and this raised no concerns with the evaluator.

Risk-benefit analysis

Delegate's considerations

Discussion

New indication for cardiovascular prevention

This indication is supported by the ODYSSEY OUTCOMES trial for secondary prevention of cardiovascular events after an index ACS in patients with hyperlipidaemia. The study design included a step for the optimisation of statin therapy, with the aim of intensive statin therapy in most patients. This is a reasonable approach given the established place of statins in lipid management and cardiovascular prevention. After approximately one year of therapy with additional alirocumab, a 15% reduction in risk for the composite primary endpoint of CV events of MI, stroke, hospital admission for unstable angina and CV death was demonstrated. This was driven primarily by a reduction in non-fatal MI, stroke and unstable angina admission. For the individual components of the primary endpoint, there was no benefit for CV or CHD death. There were multiple secondary endpoints that supported the primary endpoint. The median follow up in the study was 33 months. The survival curves were clearly divergent at this point while some patients were treated for up to 5 years, the eventual benefit after longer term therapy is an unknown.

Safety was similar to the established safety profile for alirocumab from the hyperlipidaemia clinical trial program. There was no amplification of any previous signal and similar to previous studies injection site reactions were more common than in the placebo group.

For both indications neurocognitive disorders is a relevant potential concern. The ongoing Study R727-CL-1532 aims to evaluate neurocognitive function after 96 weeks of treatment, among other endpoints. The sponsor proposes to submit this study in the EU in the second quarter of 2021. There was no apparent signal for new onset diabetes or cataract.

Taking into consideration the demonstrated benefit and safety profile from this study, the safety information to date from the hyperlipidaemia trials and the post-market safety data,

the benefit risk balance appears favourable for the use of alirocumab with optimised statins or other lipid lowering therapy for the secondary prevention of CV events.

The Delegate's preferred wording for this indication is:

> *Praluent is indicated to reduce the risk of cardiovascular events (myocardial infarction, stroke, unstable angina requiring hospitalisation) in adults with established cardiovascular disease, in combination with optimally dosed statins and/or other lipid-lowering therapies (See section 5.1 Pharmacodynamic properties, Clinical Trials)*

It takes into account the lack of apparent benefit for the reduction of CHD and CV death, and the discussion that follows regarding alirocumab monotherapy in CV prevention.

Alirocumab monotherapy

Hypercholesterolaemia

The sponsor did not submit new studies in alirocumab monotherapy to support its requested inclusion of monotherapy for the hypercholesterolaemia but requested consideration of previously provided information to be considered, in addition to the patients. Both relevant previous submissions have been considered by the Advisory Committee on Medicines (ACM) or Advisory Committee on Prescription Medicines (ACPM). A total of 178 patients were randomised to alirocumab monotherapy in this clinical trial program mostly but not exclusively with moderate CV risk. Evidence of statistically significant LDL-C lowering has been demonstrated in these studies and the effect was sustained over 4 weeks of treatment. In previous considerations of alirocumab monotherapy there was concern about its inclusion for this indication in the absence of supportive cardiovascular outcomes for alirocumab in general. Given the positive cardiovascular outcome study, while the numbers of monotherapy patients are low there may now be sufficient evidence overall to extrapolate to this group in support of monotherapy in the indication. The ACM is asked to provide advice on this matter.

Cardiovascular prevention

The evidence to support monotherapy for the cardiovascular outcomes indication is not considered sufficiently robust. Alirocumab monotherapy in the ODYSSEY OUTCOMES trial was listed as a major protocol variation, and analysis of the findings for this group was not pre-specified. This analysis lacks the rigour of the specifically designed studies provided for the hypercholesterolaemia indication and is therefore considered insufficient for inclusion in this indication.

Amended indication for hyperlipidaemia

Removal of the reference to patients with CV disease or CV risk and replacement with non-familial hypercholesterolaemia and mixed dyslipidaemia has been requested for this indication. The sponsor did not submit new studies to support its requested amendments but requested previously held information from its hyperlipidaemia development program to be reconsidered. Both relevant previous submissions have been considered by the ACM or ACPM.

In the pre-ACM response for the previous submission the sponsor noted that the Phase III studies included '5296 patients who were either heFH or non-familial hypercholesterolaemia (non-FH) patients at high CV risk including patients with other CV risk factor such as diabetes or mixed dyslipidaemia. It noted that overall 97% were at high/very high CV risk and the vast majority had atherosclerotic vascular disease. The sponsor noted that 38.2 % also had baseline TG ≥ 1.7 mmol/L (by which mixed dyslipidaemia was defined although other definitions include other lipid parameter abnormalities) and 30.8% had type II diabetes mellitus. The sponsor notes that 21.3% of the heFH patients also had elevations of triglycerides, and up to 52.2% of the patients in

high/very high CV risk studies had elevations of LDL-C and TG. The current indication already includes patients with heFH, clinical atherosclerotic cardiovascular disease, or hypercholesterolemia with high or very high cardiovascular risk. It is acknowledged that the Alternative study and the Mono study included patients with moderate CV risk.

Mixed dyslipidaemia was not an inclusion criteria of the studies in the hyperlipidaemia program or specify elevated triglycerides or other lipid abnormalities were a pre-requisite for entry, except that triglycerides > 4.5 mmol/L and a number of secondary causes of elevated triglycerides or mixed dyslipidaemia were exclusion criteria. Lipid parameters were measured but were not a primary outcome of the ODYSSEY OUTCOMES trial and the study was not specifically powered for lipid outcome assessment. While the data are supportive they are not considered pivotal to indication. In addition all patients in this study established CV disease, and would therefore those with elevated LDL-C would be included in the currently approved indication.

HeFH and non-FH therefore capture the categories of patients across the hyperlipidaemia program. There may be a case for describing the indicated population in this way, especially given the additional support for lipid lowering from the ODYSSEY OUTCOMES trial. Alternatively, the cardiovascular risk categories could be broadened to include moderate cardiovascular risk to include all patient groups studied. The Delegate's preliminary proposal for the wording for the indication is listed below, noting that the ACM is requested to comment.

> *Praluent is indicated as an adjunct to diet and exercise to reduce LDL-C in adults with one or more of: heterozygous familial hypercholesterolaemia, clinical atherosclerotic cardiovascular disease, or hypercholesterolemia with high or very high cardiovascular risk.*
>
> - *In combination with a statin, or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with 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 who are unable to reach LDL-C goals.*

Dose

The currently approved dosing regimen is proposed for the new indication and the amended current indication. Based on the data presented this is reasonable. Although not tested specifically for cardiovascular events the 300 mg every 4 weeks (Q4W) option is reasonable given that alirocumab dosing adjustments that were allowed during the ODYSSEY OUTCOMES trial.

Data deficiencies

There are no data for the prevention of CV event in patients aged < 40 years. This is noteworthy because of the indicated patients for alirocumab currently patients with compound heterozygous familial hypercholesterolaemia are at risk of CV events at an earlier age than the general population.

There are limited data in patients using alirocumab as monotherapy. Although there are more data for longer duration of therapy in the ODYSSEY OUTCOMES trial the durability of lipid lowering over the long term remains uncertain. There may be some attenuation of effect based on the data presented.

No specific study in patients with mixed dyslipidaemia has been submitted to date for alirocumab.

Summary of issues

- Whether sufficient data have been provided to support the indication to include patients with non-familial hypercholesterolaemia and/or mixed dyslipidaemia;
- Whether there is sufficient evidence to support the indication for the prevention of cardiovascular disease;
- Whether there are now sufficient data to support the expansion of use to include monotherapy in patients with hyperlipidaemia;
- Whether there is sufficient evidence to support the inclusion of monotherapy in the cardiovascular prevention indication.

Proposed action

The Delegate has no reason to say, at this time, that the application for alirocumab should not be approved for use in secondary prevention of CV events. However the Delegate is not in a position to say, at this time, that the application for alirocumab for use as monotherapy in the secondary prevention of cardiovascular events should be approved. The Delegate's proposed wording for this indication is:

> *Praluent is indicated to reduce the risk of cardiovascular events (myocardial infarction, stroke, unstable angina requiring hospitalisation) in adults with established cardiovascular disease, in combination with optimally dosed statins and/or other lipid-lowering therapies (See section 5.1 Pharmacodynamic properties, Clinical Trials).*

The Delegate is not in a position to say, at this time, that the application for alirocumab should be approved for in the management of mixed dyslipidaemia. The Delegate has no reason to say at this time that the application for alirocumab for monotherapy for the hyperlipidaemia indication should not be approved. The Delegate's proposed wording for this indication is:

> *Praluent is indicated as an adjunct to diet and exercise to reduce LDL-C in adults with one or more of: heterozygous familial hypercholesterolaemia, clinical atherosclerotic cardiovascular disease, or hypercholesterolemia with high or very high cardiovascular risk.*
>
> - *In combination with a statin, or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with 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 who are unable to reach LDL-C goals.*

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

1. Please comment on the evidence to support the sponsor's proposed new indication for the prevention of cardiovascular events.

   Please also comment on the proposed wording of the indication.

2. The sponsor has requested monotherapy with alirocumab for both the hyperlipidaemia indication and the cardiovascular prevention indication.

   Please comment on the evidence that supports this proposal.

   Does the committee have any concerns?

3. The sponsor has requested an amendment of the indication for hyperlipidaemia to remove the specific reference to clinical atherosclerotic disease and to include non-familial hypercholesterolaemia and mixed dyslipidaemia as new patient groups.

   Please comment on whether the evidence now supports the broadening of the population.

   Please specifically comment on the evidence to support mixed dyslipidaemia. Does the committee recommend alternative wording for this indication, and if so, what are the amendments recommended.

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Advisory Committee Considerations[12]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

The ACM considered the referral for advice from the TGA Delegate in relation to the submission to register Praluent prefilled syringe/prefilled pen, containing 75 mg/mL and 150 mg/mL of alirocumab.

The ACM considered this product to have an overall positive benefit-risk profile for the revised indications:

> ***Primary hypercholesterolaemia***
>
> *Praluent is indicated as an adjunct to diet and exercise to reduce LDL-C in adults with heterozygous familial or non-familial hypercholesterolaemia in patients with moderate to very high cardiovascular risk:*
>
> § *In combination with a statin, or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with maximum tolerated dose of a statin,*
>
> § *In combination with other lipid lowering therapies in patients who are statin intolerant or for whom a statin is contraindicated who are unable to reach LDL-C goals*
>
> ***Prevention of cardiovascular events***
>
> *Praluent is indicated to reduce the risk of cardiovascular events (myocardial infarction, stroke, unstable angina requiring hospitalisation) in adults with established cardiovascular disease, in combination with optimally dosed statins and/or other lipid-lowering therapies (see section 5.1 Pharmacodynamic properties, Clinical Trials).*

The ACM agreed that evidence provided in support of monotherapy was not sufficient to support the use of Praluent alone.

[12] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Specific advice

The ACM advised the following in response to the Delegate's specific request for advice.

1. ***Please comment on the evidence to support the sponsor's proposed new indication for the prevention of cardiovascular events. Please also comment on the proposed wording of the indication.***

The ACM agreed with the Delegate that the evidence in support of the cardiovascular prevention indication was sufficient to support the use of Praluent, in conjunction with other lipid lowering therapies. The ACM noted the modified cardiovascular indication proposed by the sponsor in their pre-ACM response to the Delegate's overview and agreed that this was appropriate.

2. ***The sponsor has requested monotherapy with alirocumab for both the hyperlipidaemia indication and the cardiovascular prevention indication.***

   Please comment on the evidence that supports this proposal. Does the committee have any concerns?

The ACM agreed with the Delegate that use of Praluent as monotherapy was not supported for either cardiovascular indication. The sponsor has accepted removal of the monotherapy use from the cardiovascular prevention indication in their pre-ACM response. The ACM was also of the view that the use of Praluent as monotherapy for the hyperlipidaemia indication was not supported by the evidence. No new clinical data was presented in support of monotherapy use for the primary hyperlipidaemia indication. The ACM noted the sponsor's suggestion to align the indication with evolocumab, which is indicated for monotherapy in patients that are statin intolerant. However, the ACM was of the view that the evidence supporting evolocumab monotherapy was considerably more substantial than that presented for alirocumab. The ACM was also of the opinion that there are other lipid lowering medications that could be prescribed in conjunction with alirocumab for statin intolerant patients, and that removal of the monotherapy option for the hyperlipidaemia option would therefore create no disadvantage for these patients.

3. ***The sponsor has requested an amendment of the indication for hyperlipidaemia to remove the specific reference to clinical atherosclerotic disease and to include non-familial hypercholesterolaemia and mixed dyslipidaemia as new patient groups.***

   Please comment on whether the evidence now supports the broadening of the population.

   Please specifically comment on the evidence to support mixed dyslipidaemia.

   Does the committee recommend alternative wording for this indication, and if so, what are the amendments recommended.

The ACM supported the removal of the specific reference to atherosclerotic cardiovascular disease, but advised that reference to moderate to high cardiovascular risk should remain, given that no trials have examined the evidence for treatment in the setting of low cardiovascular risk. The ACM supported the inclusion of non-familial, in addition to familial hypercholesterolaemia. The ACM advised that broadening of the indicated population to patients with mixed dyslipidaemia was not appropriate since the pivotal lipid fraction that evidence currently links to cardiovascular disease endpoints and prolonging life is low-density lipoprotein cholesterol. The ACM noted, however, that the sponsor had agreed to removal of mixed dysplipidaemia from the proposed indication in their pre-ACM response.

4. ***The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.***

Nil advised.

Follow-up advice

The Delegate subsequently consulted the ACM for a second time regarding this submission.

Further to the advice provided in the ACM meeting of August 2019, clarification was sought regarding the use of alirocumab as monotherapy in statin intolerant patients with primary hypercholesterolaemia.

General comments

The ACM noted the sponsor's request for reconsideration to expand the hypercholesterolaemia indication to include monotherapy in addition to the currently proposed combination of alirocumab with other lipid lowering therapies in patients who are statin intolerant, or for whom a statin is contraindicated who are unable to reach LDL—C goals.

The ACM further noted that based on the same data submitted in Australia, alirocumab has been approved for use as monotherapy in patients with hyperlipidaemia in Europe, the Unites States of America, Canada, Russia, Brazil, Mexico, Columbia, South Korea, Taiwan, Singapore and Israel.

The ACM noted that the sponsor had provided two studies in support of monotherapy as part of the original dossier (MONO trial (Study EFC11716), and ALTERNATIVE trial (Study R727-CL-1119)), as well as the additional data provided by the sponsor including an open label extension (OLE) of the ALTERNATIVE trial, and data from the CHOICE I trial. The ACM considered this was now sufficient evidence to justify the monotherapy indication for hypercholesterolaemia, although a larger group of patients that fitted the requested indication with provision of long term outcome data would be desirable.

The ACM disagreed with the sponsor that registration of alirocumab monotherapy would address a high unmet need for patients, since another member of the class (PCSK9 inhibitor) is already registered in Australia. The ACM was of the view that statin intolerance only affects a small proportion of patients and noted the absence of data that suggests a high number of patients are affected by both statin and ezetimibe intolerance.

The ACM noted that, depending on risk, new European Society for Cardiology guidelines recommend pharmacological LDL-C lowering to reach goals through a high intensity statin, followed by the maximum tolerated dose of a statin in combination with ezetimibe. The ACM noted that a combination with a PSCK9 inhibitor may be recommended if goals are not achieved with the initial combination, for patients at very high risk, but without familial hyperlipidaemia.

Efficacy

The ACM considered that overall, the data supported the efficacy of the alirocumab monotherapy in treatment of patients who are statin intolerant or for whom a statin is contraindicated who are unable to reach LDL-C goals, supported by data showing reduction of LDL-C by 30 to 52% following alirocumab monotherapy. In the MONO trial (Study EFC11716) the primary endpoint (% change in LDL cholesterol 0 to 24 weeks) was -54.1% at 24 weeks; in the ALTERNATIVE trial (Study R727-CL-1119) the change in LDL-C (0 to 24 weeks) was -30.4% for alirocumab; in the OLE of the ALTERNATIVE trial, the change in LDL-C from Baseline was -51.2% in Week 28 and sustained to Week 160 for alirocumab treated subjects; and in a subgroup from the CHOICE I trial (Study R727-CL-1308, the change in cholesterol was -52.4% for alirocumab. The ACM noted that these results were comparable to data in support of monotherapy with the currently registered PCSK9 inhibitor evolocumab (the MENDEL II trial), that showed a mean 40% reduction of LDL-C from Baseline to Week 12.

Safety

The ACM considered that alirocumab monotherapy was well tolerated on the basis of medium term safety data. The ACM was of a view that it was unlikely that deviation from the current safety profile would arise with the emergence of longer term data.

Specific advice

The ACM was of the view that the overall risk benefit was positive for alirocumab monotherapy in patients who are statin intolerant or for whom a statin is contraindicated who are unable to reach LDL-C goals. The ACM advised that while longer term evidence for efficacy, in a larger patient group, might be desirable, there are no notable safety concerns that should prevent registration.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the modification and extension of indications of Praluent (alirocumab (rch)) solution for injection, indicated for:

> ***Primary hypercholesterolaemia***
>
> *Praluent is indicated as an adjunct to diet and exercise to reduce LDL-C in adults with primary (heterozygous familial or non-familial) hypercholesterolaemia in patients with moderate to very high cardiovascular risk:*
>
> - *In combination with a statin, or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with a maximum tolerated dose of a statin,*
> - *Alone or in combination with other lipid-lowering therapies in patients who are statin intolerant or for whom a statin is contraindicated who are unable to reach LDL-C goals*
>
> ***Prevention of cardiovascular events***
>
> *Praluent is indicated to reduce the risk of cardiovascular events (myocardial infarction, stroke, unstable angina requiring hospitalisation) in adults with established cardiovascular disease, in combination with optimally dosed statins and/or other lipidlowering therapies (see section 5.1 Pharmacodynamic properties, CLINICAL TRIALS)*

Specific conditions of registration applying to these goods

- The Praluent EU-Risk Management Plan (RMP) (version 4.2, dated 23 January 2019, data lock point 13 February 2018), with Australian Specific Annex (version 3.1, dated

20 March 2019), included with submission PM-2018-02973-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs). Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Praluent approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

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