Common Drug Review

CADTH CANADIAN DRUG EXPERT COMMITTEE
FINAL RECOMMENDATION

Alirocumab
(Praluent – Sanofi-aventis Canada Inc.)
Indication: Primary Hyperlipidemia

For Heterozygous Familial Hypercholesterolemia

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that alirocumab be reimbursed as an adjunct to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH), who require additional lowering of low density lipoprotein cholesterol (LDL-C), if the following clinical criteria and condition are met.

Criteria:
1. Patient has a confirmed diagnosis of HeFH
2. Patient is unable to reach the target LDL-C level specified in current guidelines
3. Patient is currently receiving optimally tolerated standard of care (maximally tolerated statins (MTS) with or without ezetimibe)

Condition:
1. Reduced price

Reasons for the Recommendation:
1. Three double-blind randomized controlled trials (RCTs) of HeFH patients who had elevated LDL-C levels despite receiving optimized standard of care (FH1, FH2, and HIGH FH) and one mixed-population study of patients at high risk for CV events and/or who had elevated LDL-C levels (ODYSSEY LONG TERM) demonstrated that alirocumab (75 mg or 150 mg every two weeks) was statistically significantly superior to placebo for lowering LDL-C levels. In addition, a statistically significantly greater proportion of patients was able to achieve a prespecified LDL-C target level compared to placebo-treated patients.
2. CDEC considered alirocumab not to be cost effective at the submitted price of $279.36 per 75 mg/mL or 150 mg/mL pre-filled syringe. At this price a re-analyses of the manufacturer's pharmacoeconomic model suggested that for a mixed population with elevated LDL-C levels that comprised HeFH patients and high-risk of CV events patients, alirocumab + MTS was associated with an incremental cost-utility ratio (ICUR) of $126,375 per quality-adjusted life year (QALY) when compared to MTS alone.
   For a population of HeFH patients with elevated LDL-C levels only, the ICUR was $143,401 per QALY.

For Clinical Atherosclerotic Cardiovascular Disease

Recommendation:
CDEC recommends that alirocumab be reimbursed as an adjunct to diet and maximally tolerated statin therapy in adult patients at high risk for cardiovascular (CV) events, who require additional lowering of LDL-C, if the following clinical criteria and condition are met.

Criteria:
1. Patient is unable to reach the target LDL-C level specified in current guidelines
2. Patient is currently receiving optimally tolerated standard of care (MTS with or without ezetimibe)

Condition:
1. Reduced price

Reasons for the Recommendation:
1. Two double-blind RCTs of patients at high risk for CV events (COMBO1 and COMBO2) and one mixed-population study of patients at high risk for CV events and/or who had elevated LDL-C levels (ODYSSEY LONG TERM) demonstrated that alirocumab (75 mg or 150 mg every two weeks) was statistically significantly superior to placebo for lowering LDL-C levels. In addition, a statistically significantly greater proportion of patients was able to achieve a prespecified LDL-C target level compared to placebo-treated patients.
2. CDEC considered alirocumab not to be cost effective at the submitted price of $279.36 per 75 mg/mL or 150 mg/mL pre-filled syringe. At this price, a re-analyses of the manufacturer's pharmacoeconomic model suggested that for a mixed population with elevated LDL-C levels that comprised HeFH patients and high-risk of CV event patients, alirocumab + MTS was associated with an ICUR of $126,375 per QALY when compared to MTS alone. For a population of patients with high-risk of CV events only, the ICUR was $124,664 per QALY.

Of Note:
1. Clinical trials of alirocumab were conducted using a target LDL-C level of 1.8 mml/L. Other trials of PCSK9 inhibitors have used other LDL-C targets. CDEC recommends that current published guidelines be consulted to determine the most appropriate LDL-C targets for individual clinical situations.
2. HeFH diagnosis should be confirmed by genotyping and/or using clinical criteria such as the Simon Broome criteria or World Health Organization/Dutch Lipid Network criteria.
3. CDEC noted that a price reduction of at least 57% would be required for alirocumab to be considered to be a cost-effective treatment option in a mixed population of HeFH patients and in patients with a high risk of CV events.

Background:
Alirocumab is a monoclonal antibody that binds and inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9). Alirocumab is approved by Health Canada as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical atherosclerotic cardiovascular disease (CVD) who require additional lowering of low density lipoprotein cholesterol (LDL-C). It is available as a subcutaneous injection. The recommended starting dose is 75 mg once every 2 weeks, which can be increased to 150 mg every two weeks if the LDL-C response is inadequate.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR):

- A systematic review of pivotal and other relevant RCTs of alirocumab.
- A review of the manufacturer's pharmacoeconomic evaluation
- Information submitted by patient groups about outcomes and issues important to patients

Patient Input Information
The Heart and Stroke Foundation and Familial Hypercholesterolemia Canada Patient Network both provided input. Information was gathered via online surveys, one-on-one interviews, small group discussion via webcast, teleconference, forums and a literature search. CDEC heard:

- Some patients with hypercholesterolemia reported inadequate control with conventional therapy; others reported adequate control using statins, ezetimibe, niacin, resins, homeopathic cholesterol-sterol, coenzyme Q10 and/or acetylsalicylic acid.
- Some patients conveyed frustration and anxiety associated with the serious challenge of achieving or maintaining low cholesterol despite trying medications, low-fat diets, exercise, and other interventions.
- Fear of death, especially from the risk of stroke or cardiovascular events, was an expressed concern.
- Expectations from patients were that PCSK9 inhibitors will more effectively control their cholesterol, and that the treatment will have less adverse events, compared to statins.

Clinical Trials
The systematic review included 10 multicenter manufacturer-sponsored Phase 3 DBRCTs of patients with primary dyslipidemia. Of these trials, six were directly aligned with the manufacturer's proposed reimbursement criteria, as they included patients who were either at a high risk of CV events (COMBO1 and COMBO2), patient who had HeFH (FH1, FH2, and HIGH FH), or a mixed population of both types of patient (LONG TERM). The percent reduction in LDL-C after 24 weeks was the primary outcome of all studies.

In COMBO1, 316 primarily clinical CVD patients were randomized to either alirocumab 75 mg every 2 weeks or matched placebo over 52 weeks while in COMBO2, 720 primarily clinical CVD patients were randomized to either alirocumab 75 mg daily or ezetimibe over 104 weeks. In the FH-specific studies (FH1: N=486; FH2: N=249), patients with HeFH were randomized to either alirocumab or placebo for 78 weeks, and in HIGH FH, 107 patients were randomized to alirocumab 150 mg every 2 weeks or matched placebo for 78 weeks. In LONG TERM, a mixed population of 2,341 patients with HeFH and/or clinical CVD was randomized to either alirocumab 150 mg every 2 weeks or matched placebo for 78 weeks.

A limitation common to all of these studies was the high proportion (>20%) of patients that withdrew, although this was mitigated by the use of the mixed-effect model repeated measure method to account for missing data, and several sensitivity analyses of the primary outcome were performed in an effort to mitigate the risk of bias. Limitations related to external validity included the fact that the studies were not designed to assess important clinical outcomes such as mortality and CV morbidity, but instead assessed the surrogate outcome of changes in LDL-C levels. The change in LDL-C levels is, however, a widely accepted surrogate for these clinically relevant outcomes. Finally, none of the included studies directly compared alirocumab

to evolocumab, the other PCSK9 inhibitor approved for use in Canada, nor was there evidence in the literature to compare these two drugs indirectly. Therefore, the relative efficacy and safety of alirocumab versus evolocumab is unknown.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following:
- Mortality (all-cause and CV-related)
- Morbidity (cardiovascular-related)
- Cardiovascular events
- Hospitalizations
- Minimally-invasive cardiovascular interventions (e.g., PCI)
- Changes in LDL-C
- Quality of life
- Harms outcomes including adverse events (AE), serious AEs (SAE), and withdrawals due to AEs (WDAE)

Efficacy
FH studies

The percent reductions from baseline in LDL-C across studies ranged from 46% in HIGH FH to 49% in each of the FH1 and FH2 studies. In HIGH FH, the difference after 24 weeks between the alirocumab and placebo groups was statistically significant (LS mean [95% CI] difference between groups of -39.1% [-51.1 to -27.1] p<0.0001). This was also the case in FH1 (LS mean [95% confidence interval (CI)] difference between groups of -57.9% [-63.3 to -52.6] p<0.0001) and FH2 (LS mean [95% CI] difference between groups of -51.4% [-58.1 to -44.8] p<0.0001). The FH1 and FH2 studies also reported the proportion of patients reaching target LDL-C as a secondary outcome, either taking into account baseline CV risk (lower LDL-C target of 1.8 mmol/L for those with prior CV events and <2.6 mmol/L for those without) or not (target of <1.8 mmol/L for everyone), and these differences between alirocumab and comparators were statistically significant, where reported, in all cases. Taking into account baseline CV risk, in the alirocumab versus placebo groups, 72% versus 2% of patients reached the target LDL-C level in FH1 (OR [95% CI] of 156.0 (48.9 to 498.1) p<0.0001) and 81% versus 11% reached target in FH2 (OR [95% CI] of 52.2 (20.9 to 130.0) p<0.0001). In HIGH FH, targets were also adjusted for baseline risk (very high CV risk: <1.8 mmol/L; high CV risk: <2.6 mmol/L), and the difference between the alirocumab and placebo groups was statistically significant, with 41% of alirocumab-treated patients and 6% of placebo patients reaching target (OR [95% CI] of 11.7 (2.5 to 53.5) p=0.0016). These results suggest that treatment of HF patients with alirocumab for 24 weeks is associated with a significant reduction in LDL-C levels of between 39% and 58% versus placebo and allows significantly more patients to achieve a target LDL-C level of less than 1.8 mmol/L.

In FH 1, 2% (6 patients) of alirocumab-treated patients died versus none in the placebo group, and two of these deaths were CV-related. There was a numerically higher proportion of alirocumab- versus placebo-treated patients experiencing a CV event in the HIGH FH study (6 patients [8%] versus 0), although this was a small study and was not powered to assess this outcome in a formal manner. There were also numerically more CV events with alirocumab than

placebo in FH1 (8 [2.5%] versus 3 [1.8%] patients), but similar proportions of patients with CV events between the alirocumab and placebo groups in FH2 (2 [1%] versus 1 [1%]). Quality of life was assessed using the EQ-5D; however, this was an exploratory safety outcome and therefore not part of the hierarchy for statistical testing, and no statistically significant differences were noted between groups.

Clinical CVD studies

The percent reductions from baseline in LDL-C after 24 weeks in alirocumab-treated patients were very similar and consistent in COMBO 1 (48%) and COMBO 2 (51%). In COMBO 1, the difference after 24 weeks between the alirocumab and placebo groups was statistically significant (LS mean [95% CI] difference between groups of −45.9% [−52.5 to −39.3], p<0.0001). In COMBO 2, the difference between alirocumab and ezetimibe was also statistically significant (LS mean [95% CI] difference between groups of -29.8% [-34.4, -25.3], p<0.0001). When compared to placebo in COMBO 1, 75% alirocumab versus 9% of placebo patients achieved a target of <1.8 mmol/L (combined estimate for odds ratio [95% CI] of 38.5 [16.5 to 89.8] p<0.0001), while in COMBO 2, 77% versus 46% of patients reached this target (OR [95% CI] of 5.4 [3.7 to 7.9] p<0.0001). These results suggest that treatment of patients at a high risk of CV events with alirocumab for 24 weeks is associated with a significant reduction in LDL-C levels of 30% to 46% versus ezetimibe or placebo and allows significantly more patients to achieve a target LDL-C level of less than 1.8 mmol/L.

There were no consistent differences in the number of deaths between treatments within each study. The proportion of patients with a CV event was similar for the alirocumab and placebo groups in COMBO 1 (6 [2.9%] versus 3 [2.8%]) and for the alirocumab and ezetimibe groups in COMBO 2 (23 [4.8%] versus 9 [3.7%]).

Quality of life was assessed using the EQ-5D; however, this was an exploratory safety outcome and no statistically significant differences were noted between groups.

Mixed population study

In ODYSSEY LONG TERM, there was a statistically significantly greater percent reduction in LDL-C for alirocumab versus placebo after 24 weeks (LS mean [95% CI] difference between groups of -61.9% [-64.3, -59.4], p<0.001). The ODYSSEY LONG TERM study also reported the proportion of patients reaching target LDL-C as a secondary outcome, either taking into account baseline CV risk (lower LDL-C target of <1.8 mmol/L for those with prior CV events and <2.6 mmol/L for those without) or not (target of <1.8 mmol/L for everyone) and these differences between the alirocumab and placebo groups were statistically significant, where reported, in both cases. Taking into account baseline CV risk, in the alirocumab versus placebo groups 81% versus 9% of patients reached target (OR [95% CI] of 71.5 (51.6 to 99.1) p<0.0001) while 79% versus 8% reached target when baseline CV risk was not taken into account (OR [95% CI] of 74.6 (53.3 to 104.4) p<0.0001). These results suggest that treatment of patients with FH and/or high CV risk with alirocumab for 24 weeks is associated with a significant reduction in LDL-C levels of up to 62% versus placebo and allows significantly more such patients to achieve a target LDL-C level of less than 1.8 mmol/L.

In ODYSSEY LONG TERM, 8 (0.5%) alirocumab- and 10 (1.3%) placebo-treated patients died, respectively, while CV deaths occurred in 4 (0.3%) alirocumab- and 7 (0.9%), placebo-treated

patients, respectively. CV events in ODYSSEY LONG TERM occurred in 72 (4.6%) alirocumab-treated patients and 40 (5.1%) placebo patients.

Harms
Clinical CVD studies
Alirocumab treatment did not appear to be associated with a substantial risk of potential harm in patients with clinical CVD. The proportion of patients experiencing any AE was similar between the alirocumab and placebo groups in COMBO 1 (76% in each group after 52 weeks) and COMBO 2 (71% versus 67% after 104 weeks). Upper respiratory tract infection and dizziness were common AE across studies, but these events were infrequent (5% to 7% of patients). The most common notable harm in both studies was an allergic event, which occurred in 5% to 9% of patients across studies. The proportion of patients experiencing an SAE was similar between the alirocumab and placebo groups in COMBO 1 (13% in each group after 52 weeks) and alirocumab versus ezetimibe in COMBO 2 (19% versus 18% after 104 weeks). In COMBO 1, WDAE occurred in 6% of alirocumab-treated patients and 8% of placebo patients, and in COMBO 2, WDAE occurred in 8% of alirocumab-treated patients and 5% of ezetimibe patients.

FH studies
Alirocumab treatment did not appear to be associated with a substantial risk of potential harm in HF patients. The proportion of patients with an AE after 78 weeks was numerically lower in the alirocumab treatments arm versus placebo in FH2 (75% versus 82%) and HIGH FH (61% versus 71%), and similar between the groups in FH2 (82% versus 79% for alirocumab and placebo, respectively). The most common AE across studies was nasopharyngitis. The most common notable harm across the FH studies was injection site reaction, and there was a larger proportion of alirocumab- versus placebo-treated patients in HIGH FH (8% versus 3%) with this AE. The proportion of patients experiencing an SAE was similar between alirocumab versus placebo in FH1 (14% in each after 78 weeks), FH2 (9% in alirocumab, 10% in placebo after 78 weeks) and HIGH FH (11% in each after 78 weeks). In FH1, WDAE occurred in 3% of alirocumab versus 6% of placebo patients, in FH2 WDAE occurred in 4% of alirocumab versus 1% of placebo patients and in HIGH FH, 4% of alirocumab versus 3% of placebo patients.

Mixed population study
Alirocumab treatment did not appear to be associated with a substantial risk of potential harm in patients with HF and/or with clinical CVD. In ODYSSEY LONG TERM, 81% of alirocumab versus 83% of placebo patients experienced an AE after 78 weeks. The most common AE was nasopharyngitis. The most common notable harm was allergic reaction, occurring in 10% of alirocumab and placebo patients. There were similar proportions of alirocumab- versus placebo-treated patients experiencing an SAE in ODYSSEY LONG TERM (19% versus 20% after 78 weeks). WDAE occurred in 7% of alirocumab versus 6% of placebo patients in ODYSSEY LONG TERM.

Cost and Cost-Effectiveness
The submitted price for alirocumab is $279.36 per 75 mg/mL or 150 mg/mL pre-filled syringe. At the recommended dose of 75 mg or 150 mg administered once every two weeks, alirocumab costs $7,263 per year.

The manufacturer submitted a cost-utility analysis comparing alirocumab as an add-on to MTS versus MTS alone, in a mixed cohort with uncontrolled LDL-C consisting of patient with: HeFH

(including subgroups patients with HeFH treated for the primary and secondary prevention of CV events); and, high-risk with previous CV events (consisting of subgroups of patients with an ACS during the previous 0-12 months, with an ACS during the previous 13-24 months, with a history of ischemic stroke (IS), and those with other CHD). The effects of treatment were assessed by linking treatment efficacy in terms of percent reduction in LDL-C to the occurrence of fatal and non-fatal CV events. Treatment efficacy in terms of LDL-C reduction was obtained from the ODYSSEY clinical trial program. The relationships between reduction in LDL-C level and risk of CV outcomes were derived from meta-analyses of clinical trials that included lipid-based and clinical outcomes. Baseline patient characteristics were informed by a primary care longitudinal cohort from the UK (the THIN database) and observed characteristics of Canadian statin users. The analysis was undertaken from a Canadian public payer perspective over a lifetime horizon.

CDR identified the following key limitations of the manufacturer's economic submission:
- The manufacturer used different meta-analyses for the alirocumab + MTS and MTS alone populations to inform the relationship between LDL-C and risk of CV outcomes, implying that lowering cholesterol exerts different effects on CV risk depending on the medication used. This assumption is unsubstantiated and serves to bias estimates of cost effectiveness in favour of alirocumab.
- The manufacturer considered inappropriate minimum LDL-C cut-offs for HeFH secondary prevention patients and high-risk CV patients with 'other coronary heart disease', which corresponded to less severe patient populations than the ones to be assessed.
- Overestimation of CV death costs biased results in favour of alirocumab.
- Use of a time horizon that is longer than warranted given the uncertainty in the manufacturer's assumption of ODYSSEY LONG TERM maintenance of treatment effect (LDL-C lowering), until the end of the model time horizon.

Based on CDR re-analyses to account for the above limitations (i.e., use of the same data linking LDL-C reduction to risk of CV events regardless of treatment; correction of LDL-C cut-off values for treatment initiation; reduction of costs of CV mortality by 50%; and, reduction of the model time horizon to 20 years), for the mixed cohort of HeFH patients and high-risk patients with previous CV events, alirocumab + MTS was associated with an ICUR of $126,375 per QALY when compared to MTS alone, driven by the relationship between LDL-C level and risk of CV outcomes. For HeFH patients only, the ICUR was $143,401 per QALY (ranged from $60,092 to $190,006 per QALY for the subgroups). For the high-risk patients with previous CV events, the ICUR was $124,664 per QALY (ranged from $86,005 to $138,310 per QALY for the subgroups). Based on the CDR's best estimate of $126,375 per QALY for the mixed cohort, a price reduction of 20% would be required for the ICUR of alirocumab + MTS versus MTS alone to fall below $100,000 per QALY and of 57% to fall below $50,000 per QALY.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:
- The effect of alirocumab on cardiovascular morbidity and mortality has not been determined.
- The longer-term safety and efficacy profile of alirocumab requires further evaluation.
- The comparative efficacy of alirocumab and evolocumab for reduction of CV endpoints requires assessment.

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini,
Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson,
Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers,
Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

June 15, 2016 Meeting

Regrets:
None

Conflicts of Interest:
None

About this Document:
CDEC provides formulary listing recommendations or advice to CDR participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

The Canadian Agency for Drugs and Technologies in Health (CADTH) is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.