Common Drug Review
Pharmacoeconomic Review Report

July 2016

Drug	Alirocumab (Praluent)
Indication	Indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C). The effect of Praluent on cardiovascular morbidity and mortality has not been determined.
Listing request	As an adjunct to diet and maximally tolerated statin (MTS) therapy with or without other lipid-lowering therapies (LLT), Praluent should be reimbursed for adults with HeFH or high-risk patients who have had prior cardiovascular (CV) events and require additional lowering of LDL-C. Prior CV events include myocardial infarction (MI), unstable angina (UA) requiring hospitalization, coronary revascularization, and ischemic stroke.
Dosage form(s)	75 mg/mL and 150 mg/mL pre-filled syringe
NOC date	April 11, 2016
Manufacturer	Sanofi-Aventis Canada Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

ACS	acute coronary syndrome
CDR	CADTH Common Drug Review
CV	cardiovascular
CHD	coronary heart disease
CTTC	Cholesterol Treatment Trialists' Collaboration
HeFH	heterozygous familial hypercholesterolemia
EZE	ezetimibe
ICUR	incremental cost-utility ratio
LDL-C	low-density lipoprotein cholesterol
MTS	maximally tolerated statin
PCSK9	proprotein convertase subtilisin/kexin type 9
QALY	quality-adjusted life-year
THIN	The Health Improvement Network, UK

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	**Alirocumab (Praluent)**
Study Question	"The objective of this study was to conduct a Canadian-specific economic evaluation of alirocumab aligned to Sanofi's anticipated Health Canada indication and reimbursement ask. Sanofi requests the following listing criteria for alirocumab: as an adjunct to diet and MTS ± other LLT for the treatment of adults with HeFH or high-risk patients who have had prior CV events and require additional lowering of LDL-C. Prior CV events include MI, unstable angina requiring hospitalization, coronary revascularization, and ischemic stroke."
Type of Economic Evaluation	Cost-utility analysis
Target Population	A mixed cohort of patients with HeFH and patients at high risk for CV events, consisting of patients with prior CV events who require additional lowering of lowering of LDL-C HeFH patients included: • Primary prevention • Secondary prevention High-risk CV patients included: • Patients with ACS in the last 0 to 12 months • Patients with ACS (13 to 24 months) • Patients with history of IS • Patients with other CHD
Treatment	Alirocumab 75 mg or 150 mg once every two weeks, adjunctive to diet and MTS therapy (consisting of rosuvastatin 20 mg to 40 mg, atorvastatin 40 mg to 80 mg, or simvastatin 80 mg daily)
Outcomes	Quality-adjusted life-years (QALYs) Life-years (LYs)
Comparators	MTS alone MTS + ezetimibe (considered as an additional comparator)
Perspective	Canadian public payer
Time Horizon	Lifetime (up to patient age of 99 years); the mean age of the modelled cohort was 66
Results for Manufacturer's Base Case	ICURs for alirocumab + MTS vs. MTS alone: • $46,416 per QALY • $46,111 per LY ICURs for patient subgroups ranged from $32,502 per QALY (HeFH – secondary prevention) to $87,279 per QALY (HeFH – primary prevention).
Key Limitations	• The data used to model treatment effects of LDL-C lowering on reduction of CV events were different for alirocumab + MTS and MTS alone. This is inappropriate and biases results in favour of alirocumab. CDR applied the same data for both patient groups in reanalysis. • The minimum LDL-C level required for treatment initiation for HeFH secondary prevention patients and high-risk CV patients with "other CHD" may not be reflective of clinically appropriate values. Patients with "other CHD" were assumed to initiate treatment at 3.4 mmol/L (reflective of an intermediate-risk population) rather than the 2.6 mmol/L minimum cut-off for a high-risk population. Similarly, HeFH patients treated for secondary prevention were assumed to require values of 2.6 mmol/L for treatment initiation (reflecting a high-risk population) while 1.8 mmol/L (reflective of a very high-risk population) would be more appropriate. This biases the results in favour of alirocumab, and was accounted for in CDR reanalyses.

	• All patients who died of CV causes incurred a cost of dying (including in-patient care). Considering that the CDR clinical expert indicated that ~ 50% of such CV deaths happen in hospital, this cost may have been overestimated in favour of alirocumab given that fewer CV deaths are expected in the alirocumab group. CDR reanalyses reduced this cost by 50%. • There is uncertainty about the assumption of long-term durability of effect in terms of LDL-C lowering with alirocumab. This was explored by CDR by changing the time horizon to 20 years.
CDR Estimates	• Based on the reanalysis addressing the above limitations, CDR found alirocumab adjunctive to diet and MTS is associated with an ICUR of $126,375 per QALY when compared with MTS alone, driven by assumptions regarding the relationship between LDL-C levels and CV risk. • A price reduction of more than 57% would be required for alirocumab to be cost-effective at a willingness-to-pay threshold of $50,000 per QALY for a mixed population of HeFH and high-risk CV patients. • ICURs for patient subgroups ranged from $60,092 per QALY (HeFH – secondary prevention) to $190,006 per QALY (HeFH – primary prevention). • ICURs for high-risk CV patient subgroups ranged from $86,005 per QALY (ACS 0 to 12 months) to $138,310 per QALY (other CHD).

ACS = acute coronary syndrome; CHD = coronary heart disease; CDR = CADTH Common Drug Review; CV = cardiovascular; HeFH = heterozygous familial hypercholesterolemia; ICUR = incremental cost-utility ratio; IS = ischemic stroke; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; LY = life-year; MI = myocardial infarction; MTS = maximally tolerated statin therapy; QALY = quality-adjusted life-years; vs. = versus.

EXECUTIVE SUMMARY

Background

Alirocumab (Praluent) is a fully human monoclonal proprotein convertase subtilisin/kexin type 9 (PCSK9) antibody that acts as a cholesterol-lowering drug.[1] Alirocumab is indicated as an adjunct to diet and maximally tolerated statin (MTS) therapy among patients with primary hypercholesterolemia (non-familial or heterozygous familial hypercholesterolemia [HeFH]) or mixed dyslipidemia to decrease low-density lipoprotein cholesterol (LDL-C). The manufacturer is requesting reimbursement of alirocumab for a population of adult patients with HeFH or patients at high risk for cardiovascular (CV) events who have had prior CV events and require additional lowering of LDL-C. Prior CV events include myocardial infarction, unstable angina requiring hospitalization, coronary revascularization (e.g., percutaneous coronary intervention or coronary artery bypass grafting), and ischemic stroke.

The manufacturer submitted a market price of $279.36 per 75mg/mL or 150 mg/mL pre-filled syringe. At a recommended dose of 75 mg or 150 mg administered once every two weeks, alirocumab costs $7,263 annually.

The manufacturer submitted a cost-utility analysis comparing alirocumab as an add-on to diet and MTS (consisting of medium-intensity or high-intensity statins, defined as rosuvastatin 20 mg to 40 mg, atorvastatin 40 to 80 mg, or simvastatin 80 mg daily) compared with MTS alone in a mixed cohort of HeFH patients and high-risk patients with previous CV events and uncontrolled LDL-C. The analysis was based on a lifetime time horizon (patients' mean age at model entry = 66) and was undertaken from the Canadian public payer perspective.[2] The general principle of the model was to link the primary end point of percentage reduction in LDL-C observed in relevant trials from the ODYSSEY clinical trial program[3] (further details in Table 8) with the occurrence of fatal and non-fatal CV events. The relationship between reduction in LDL-C levels and risk reduction in CV events was derived from meta-analyses of clinical trials that included lipid-based and clinical outcomes.[4,5] The model structure, illustrated by Figure 1, considered baseline patient characteristics taken from a primary care longitudinal cohort from the UK (The Health Improvement Network [THIN] database) and observed characteristics of Canadian statin users.[6,7] The manufacturer reported that, when compared with treatment with MTS alone, alirocumab + MTS has an incremental cost-utility ratio (ICUR) of $46,416 per quality-adjusted life-year (QALY).

Summary of Identified Key Limitations

CADTH Common Drug Review (CDR) noted several limitations with the manufacturer's economic submission. Modelling of treatment effects relied on linking treatment efficacy in terms of LDL-C lowering to reductions in the risk of subsequent CV events based on meta-analyses of trials. The manufacturer used different meta-analyses for the alirocumab[4] and MTS[5] populations, 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.

Further limitations include the following: inappropriate minimum LDL-C cut-offs for HeFH secondary prevention patients and high-risk CV patients with "other coronary heart disease (CHD)" corresponding to patient populations less severe than the ones to be assessed; uncertainty in the data used to inform utility values; overestimation of the costs of mortality for CV-specific causes; and use of a time horizon that is longer than warranted given uncertainty in treatment effect maintenance.

Key Results and Conclusions

When addressing the identified limitations by considering the same data linking LDL-C levels to risk of CV events for both patient populations, by using an LDL-C cut-off for treatment initiation reflecting the high-risk and very-high-risk status of "other CHD" and HeFH secondary prevention patients respectively, by reducing by 50% the cost of CV mortality, and by reducing the model time horizon to 20 years, CDR estimated that the ICUR for adjunctive alirocumab + MTS compared with MTS alone was $126,375 per QALY, driven by the relationship between LDL-C levels and risk of CV outcomes. The ICURs for patient subgroups ranged from $60,092 per QALY (HeFH – secondary prevention) to $190,006 per QALY (HeFH – primary prevention) (details in Table 14).

Based on CDR's estimate, 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 a price reduction of more than 57% would be required to fall below $50,000 per QALY in a mixed population of HeFH and high-risk CV patients.

Notably, the comparative cost-effectiveness of alirocumab versus evolocumab is unknown and may become of interest for plans aiming to reimburse evolocumab based on a recent positive reimbursement recommendation from CADTH's Canadian Drug Expert Committee.[8]

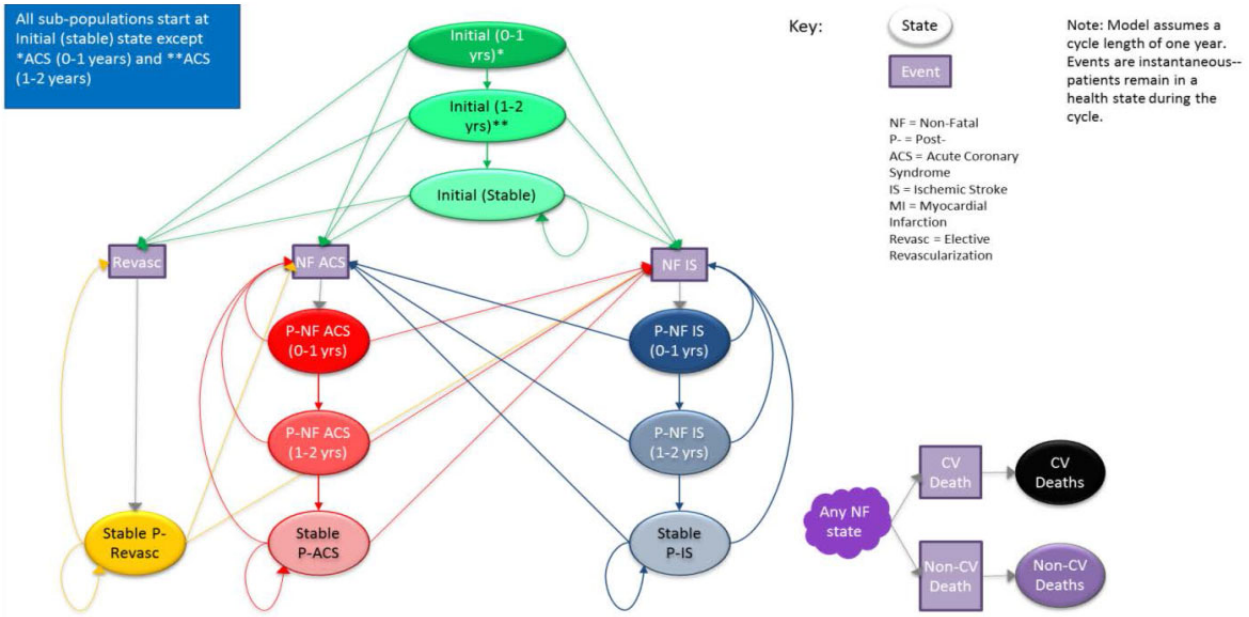
INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis comparing alirocumab (added to diet and background maximally tolerated statin [MTS] therapy, consisting of rosuvastatin 20 mg to 40 mg, atorvastatin 40 mg to 80 mg, or simvastatin 80 mg daily) with MTS alone among a cohort of patients with heterozygous familial hypercholesterolemia (HeFH) or at high risk of cardiovascular (CV) events, reflecting the manufacturer's proposed reimbursement request. The cohort consisted of a mixed population of HeFH patients and high-risk CV patients (i.e., those with previous CV events and uncontrolled low-density lipoprotein cholesterol [LDL-C] despite MTS). Patients in the starting cohort were classified into five categories: HeFH (secondary and primary prevention), acute coronary syndrome (ACS, consisting of myocardial infarction or unstable angina) within the last 0 to 12 months, history of ischemic stroke, ACS within the last 13 to 24 months, and other coronary heart disease (CHD, defined as experiencing ACS ≥ 2 years previous or other evidence of established CHD). The composition of the cohort was derived from The Health Improvement Network (THIN) cohort in the UK. Further details about the characteristics of the cohort and of each CV risk category (including the proportion with diabetes, the baseline LDL-C level, and the minimum LDL-C cut-off for treatment initiation) are available in Table 8**.** CV risk categories were used to inform the baseline risk of subsequent CV events and baseline utilities. The starting cohort was assumed to be 60% male (reflecting the proportion in the UK THIN cohort) and 66 years old (reflecting the average age of statin users in Canada).[7] The analysis was undertaken from the perspective of the Canadian public payer and considered a lifetime horizon (i.e., up to a patient age of 99).

The cost-utility analysis was based on a Markov model in which patients entered in an initial health state and could subsequently remain in their initial state, experience CV events, or die from CV or other causes (Figure 1). The model used one-year cycles and applied a half-cycle correction. Patients entered the model assigned to one of three initial mutually exclusive states depending on their CV risk category: ACS in the previous zero to one years, ACS within the last one to two years, and initial stable CV disease (starting state for HeFH, ischemic stroke, and other CHD CV risk categories). Patients in any of the initial states were at risk of experiencing CV events, including revascularization, an ACS event, or an ischemic stroke. After experiencing an event, patients moved to post-event states where they remained until experiencing further events or dying. For ACS and ischemic stroke events, patients initially moved through acute post-event states (0 to 1 years and 1 to 2 years post-event, during which there was higher probability of event recurrence) before entering a chronic, stable post-event state. Baseline risk for CV events was based on CV risk category and informed by the observed event rates in the UK THIN cohort. The treatment effects were assessed by combining treatment efficacy in terms of LDL-C lowering to relative risk reductions in CV events. Efficacy in terms of LDL-C lowering was derived from the pooled results of trials from the ODYSSEY clinical trial program (details in Table 8), and the relationship between LDL-C lowering and CV risk reduction was informed by meta-analyses linking LDL-C reductions to relative risk reductions for CV events. Separate meta-analyses were used for alirocumab patients (Navarese et al.)[4] and MTS patients (the Cholesterol Treatment Trialists' Collaboration [CTTC] meta-analysis)[5]. Rates of mortality due to CV causes was based on observed deaths in the UK THIN cohort, and age-specific and sex-specific all-cause mortality rates were derived from Statistics Canada data.[9-11]

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE



ACS = acute coronary syndrome; IS = ischemic stroke; MI = myocardial infarction; NF = non-fatal; P- = post; Revasc = elective revascularization.
Source: Manufacturer's pharmacoeconomic submission.[2]

Patients incurred costs and quality-adjusted life-years (QALYs) based on the health states they passed through and their initial CV risk category. Baseline utilities for each subgroup were based on directly measured EuroQoL 5-Dimension Questionnaire utilities recorded at week 0 from a pooled analysis of alirocumab trials. Acute-event disutilities and post-event utilities were based on values used by the National Institute for Health and Care Excellence (NICE) in their lipid modification guidelines.[12] Costs considered were drug costs and the costs associated with CV events. The cost of alirocumab was taken from the manufacturer's submitted market price. The costs of MTS were based on a weighted average of Ontario Drug Benefit formulary prices for the individual statins used in the types and proportions observed in the ODYSSEY trials. Costs associated with health care–related CV events (including death due to CV causes) included costs of emergency room visits, hospitalizations, follow-up, and medication. These were informed by data from previous CADTH reports[13-15] and other Canadian literature.[16]

Refer to Table 8, Table 9, and Table 10 for more information about the cohort composition, the data sources, and the manufacturer's key assumptions.

2. MANUFACTURER'S BASE CASE

From the public payer perspective, the manufacturer reported in its base-case analysis that alirocumab is associated with a cost of $48,864, 9.86 life-years, and 8.40 QALYs for a mixed population of HeFH and high-risk CV patients. When compared with MTS alone, alirocumab was $32,522 more costly and associated with 0.71 additional life-years and 0.70 additional QALYs, for incremental cost-effectiveness ratio (ICERs) of $46,111 per life-year and $46,416 per QALY (incremental cost-utility ratios [ICURs] for patient subgroups ranged from $32,502 per QALY [HeFH – secondary prevention] to $87,279 per QALY [HeFH – primary prevention]) (details in Table 11).

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

Among the manufacturer's reported one-way sensitivity analyses, the relationship between reduction in LDL-C levels and relative risk reduction in CV events (variation of rate ratios linking LDL-C reductions and CV event reductions), baseline LDL-C levels, initial age, and CV risk level were all found to impact ICURs. Of these, the sensitivity analysis for relationship between reduction in LDL-C levels and relative risk reduction in CV events demonstrated the largest impact on cost-effectiveness estimates, with ICURs from the public payer perspective ranging from $32,948 per QALY to alirocumab + MTS being dominated by MTS alone.

The manufacturer reported the results of a probabilistic sensitivity analysis, in which the ICUR for alirocumab + MTS versus MTS alone is less than $50,000 per QALY in 52% of simulations. Despite the ICUR of $46,416 per QALY reported by the manufacturer in its base case, there is a fifty-fifty chance that the ICUR will be greater than $50,000.

The manufacturer also reported sensitivity analyses comparing alirocumab + MTS with ezetimibe + MTS, reporting an ICUR of $66,169 per QALY. Ezetimibe use is low in Canada (accounting for 6% of all lipid-lowering therapies sold in 2014),[2] and as such was not the focus of the CADTH Common Drug Review (CDR) report (full details provided in Table 12).

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

Assumption that equivalent LDL-C reductions produce different reductions in risk of CV events depending on whether alirocumab or MTS is used

The manufacturer used different meta-analyses to link treatment efficacy (in terms of LDL-C lowering, as in the alirocumab trials) to reductions in CV outcomes (i.e., Navarese et al.'s meta-analysis[4] for alirocumab patients and the CTTC meta-analysis[5] for MTS patients). This suggests that lowering cholesterol results in different effects on CV risk depending on the medication used. Each 1 mmol/L reduction in LDL-C produces a greater risk reduction in Navarese et al.'s meta-analysis than in the CTTC meta-analysis, which biases the results in favour of alirocumab.

- The assumption that each 1 mmol/L reduction in LDL-C produces a different risk reduction that depends on how the reduction was achieved is unsubstantiated. In the absence of clinical or physiologic evidence, it would have been more appropriate to use the same values for alirocumab and MTS patients. Further, best practice in health economics is that the relationship between the surrogate and final outcomes is not treatment dependent.
- Methodological problems in Navarese et al.'s meta-analysis have led some authors to consider their estimated risk ratios to be overly optimistic.[17,18] The use of different meta-analyses for alirocumab + MTS and MTS alone serves to bias cost-effectiveness estimates in favour of alirocumab.

For CDR reanalysis, values from the CTTC meta-analysis[5] were used for both alirocumab patients and MTS patients to address this limitation.

Minimum LDL-C cut-off for treatment initiation in the HeFH (secondary prevention) and "other CHD" CV risk groups may not be reflective of clinically appropriate values

In two patient groups, inappropriate minimum LDL-C cut-off levels for treatment initiation were used in the manufacturer's base case:

- High-risk CV patients in the "other CHD" group required a minimum LDL-C level of 3.4 mmol/L for treatment initiation in the manufacturer's base case; this corresponds to the levels for a population

at intermediate risk of CV events as per the 2012 Canadian Cardiovascular Society guidelines.[19] This difference is problematic considering that the population of interest is patients at high risk of CV events, and the "other CHD" subgroup represents a high-risk subgroup given that they are a secondary prevention cohort with established CHD. This characteristic is in contrast to that of intermediate-risk patients, who lack high-risk factors such as established CHD.

- HeFH patients requiring treatment for secondary prevention initiated treatment at an LDL-C level of 2.6 mmol/L, reflecting a high-risk population. However, as noted in the published ODYSSEY familial hypercholesterolemia (FH) 1 and FH 2 trials,[20] HeFH secondary prevention patients are a very-high-risk population for whom a target LDL-C of 1.8 mmol/L is more appropriate. A 1.8 mmol/L cut-off for LDL-C among very-high-risk patients is further proposed by the Canadian Cardiovascular Society guidelines[19] and the European Atherosclerosis Society's consensus statement on the treatment of familial hypercholesterolemia.[21]

To address this limitation, the CDR reanalysis used LDL-C cut-offs of 2.6 mmol/L and 1.8 mmol/L for the "other CHD" and HeFH secondary prevention groups, reflecting risk-appropriate values.

Uncertainty in data used to estimate utility values

The manufacturer used patient-reported EuroQoL 5-Dimension Questionnaire utilities from a pooled analysis of the ODYSSEY FH 1, FH 2, HIGH FH, COMBO 1, COMBO 2, and LONG TERM clinical trials to inform baseline health state utilities in its base-case analysis. This may be questionable because there is heterogeneity in the underlying study populations. Notably, patients differed across trials in their diagnoses (HeFH versus high-risk CV), baseline use of high-intensity statins, age, baseline LDL-C levels, and proportion with a history of myocardial infarction or ischemic stroke (see CDR Clinical Report). The heterogeneity in patient baseline characteristics across trials introduces uncertainty into QALY estimates.

Mortality costs are considered for all CV-related deaths

The costs associated with health care–related CV events included the cost of emergency room visits, in-patient and outpatient hospitalizations, follow-up care, home care or long-term care, and medication. The manufacturer also considered the costs of death incurred by patients dying from CV causes ($9,930.51, which was a weighted average of the costs associated with fatal myocardial infarction [$10,164.26] and fatal stroke [$9,563.84]). Considering that the CDR clinical expert indicated that about 50% of such CV deaths happen in hospital, this cost was judged to be overestimated in favour of alirocumab given that fewer CV deaths are expected in the alirocumab group. CDR reanalyses reduced this cost by 50%.

Length of model time horizon associated with uncertainty given lack of long-term evidence of treatment efficacy

Although the use of a lifetime horizon is appropriate for chronic diseases, a lack of long-term evidence for comparative effectiveness of the treatment options makes the manufacturer's extrapolation of treatment effects uncertain, especially the assumption that efficacy in terms of LDL-C lowering is maintained over a lifetime horizon. To address this limitation, the CDR reanalysis used considered a time horizon of 20 years.

5. CADTH COMMON DRUG REVIEW REANALYSES

To account for the limitations identified above, CDR undertook the following analyses:

1. **Use of CTTC meta-analysis to link LDL-C reductions and CV outcomes**
   The CTTC meta-analysis was used in both the alirocumab + MTS and MTS alone groups to account for the initial use of two different meta-analyses.
2. **Corrected LDL-C cut-off values**
   Minimum LDL-C cut-offs for treatment initiation were changed to reflect risk-group appropriate values for HeFH secondary prevention patients (changed from 2.6 mmol/L to 1.8 mmol/L, reflecting very-high-risk patients) and high-risk CV patients with other CHD (changed from 3.4 mmol/L to 2.6 mmol/L, reflecting high-risk patients) based on Canadian Cardiovascular Society guidelines[21] and the European Atherosclerosis Society's consensus statement on familial hypercholesterolemia[21] and confirmed in the published ODYSSEY FH 1 and FH 2 studies.[20]
3. **Reduction of the costs of CV deaths**
   The cost of CV deaths was reduced by 50%.
4. **20-year horizon**
   A 20-year time horizon was considered to rectify uncertainty in long-term efficacy estimates.

TABLE 2: SUMMARY OF CDR REANALYSES

Scenario		ICUR ($ per QALY) for Alirocumab + MTS vs. MTS alone
	Manufacturer's Base Case	*$46,416*
1	Use of CTTC meta-analysis to link LDL-C reductions and CV outcomes	$95,706
2	Corrected LDL-C cut-off values	$54,203
3	50% cost of CV deaths	$46,865
4	20-year horizon	$49,734
1 to 4	**CDR best estimate**	**$126,375**

CDR = CADTH Common Drug Review; CTTC = Cholesterol Treatment Trialists' Collaboration; CV = cardiovascular; ICUR = incremental cost-utility ratio; LDL-C = low-density lipoprotein cholesterol; MTS = maximally tolerated statin therapy; QALY = quality-adjusted life-year; vs. = versus.

Refer to Table 13, Table 14, and Table 15 for more detailed results, for the results of the different subgroups included in the mixed population assessed by the model, and for CDR results for the comparison of alirocumab + MTS versus ezetimibe + MTS.

6. CADTH COMMON DRUG REVIEW PRICE REDUCTION ANALYSIS

When considering the CDR best estimate for a mixed population, 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 a price reduction of more than 57% to fall below $50,000 per QALY (Table 14).

TABLE 3: CDR REANALYSIS PRICE REDUCTION SCENARIOS

ICURs of Alirocumab vs. MTS	
Price	**CDR Best Estimate**
Submitted ($279.36/syringe[a])	$126,375
10% reduction ($251.42/syringe)	$112,979
20% reduction ($223.49/syringe)	$99,582
30% reduction ($195.55/syringe)	$86,185
40% reduction ($167.62/syringe)	$72,788
50% reduction ($139.68/syringe)	$59,391
55% reduction ($125.71/syringe)	$52,693
57% reduction ($120.13/syringe)	$50,014
60% reduction ($111.74/syringe)	$45,995
65% reduction ($97.78/syringe)	$39,296
70% reduction ($83.81/syringe)	$32,598

ICUR = incremental cost-utility ratio; MTS = maximally tolerated statin therapy; vs. = versus.
[a] 75 mg/mL or 150 mg/mL.

A price reduction of more than 15% would be required for the ICUR of alirocumab + MTS versus MTS alone to fall below $50,000 per QALY for the most cost-effective subgroup of patients (HeFH – secondary prevention). Price reductions of more than 45% and more than 70% would be necessary for the ICUR to fall below $100,000 per QALY and $50,000 per QALY, respectively, among the least cost-effective subgroup of patients (HeFH — primary prevention).

7. ISSUES FOR CONSIDERATION

Evolocumab (Repatha) is another PCSK9 inhibitor that received a positive reimbursement recommendation from the CADTH Canadian Drug Expert Committee in January 2016.[8] At the time of this review, evolocumab was not reimbursed by any participating drug plan. Although there is a lack of direct or indirect comparisons with PCSK9 inhibitors, the comparison of alirocumab with evolocumab will be of interest to jurisdictions.

8. PATIENT INPUT

Input was received from the Heart and Stroke Foundation and the Familial Hypercholesterolemia Canada Patient Network. Patients noted that it was challenging and often frustrating to maintain low cholesterol. The intensive medication regimens with occasionally severe side effects, frequent medical appointments, and heightened anxiety regarding the prospect of premature fatal or non-fatal CV events have a significant impact on quality of life and the activities of daily living. These were partially accounted for in the economic evaluation through inclusion of utility weights based on medical history. Furthermore, concerns were voiced about the large number of medications necessary as well as the attendant side effects and the difficulties of diet and exercise. These concerns can impact compliance as considered in the economic model.

9. CONCLUSIONS

After addressing the identified limitations (by considering the same LDL-C and CV events correlation data for comparing treatment groups in the model, appropriate minimum LDL-C cut-offs for treatment initiation in accordance with the characteristics of the population at high risk of CV events, removing the costs of CV mortality, and reducing the model time horizon to 20 years), CDR estimated that the ICUR for adjunctive alirocumab + MTS compared with MTS alone was $126,375 per QALY.

Based on this estimate, 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 a price reduction of more than 57% would be needed for the ICUR to fall below $50,000 per QALY in a mixed population of HeFH and high-risk CV patients.

The cost-effectiveness of alirocumab versus evolocumab is unknown.[8]

APPENDIX 1: COST COMPARISON

The comparators presented in the table below have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice rather than actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are manufacturer list prices unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and therefore the table may not represent the actual costs to public drug plans.

TABLE 4: COST COMPARISON TABLE FOR TREATMENTS USED FOR THE TREATMENT OF PRIMARY HYPERLIPIDEMIA OR MIXED DYSLIPIDEMIA

Drug / Comparator	Strength	Dosage Form	Price ($)	Dosage	Annual Cost ($)
Alirocumab (Praluent)	**75 mg/mL 150 mg/mL**	**pre-filled syringe**	**279.3600[a]**	**75 mg or 150 mg SC injection every 2 weeks**	**7,263**
Anti-PCSK9 Monoclonal Antibody					
Evolocumab (Repatha)	140 mg/mL	pre-filled syringe	279.3560[b]	140 mg SC injection every 2 weeks **or** 420 mg every month[c]	7,263 to 10,895
HMG-CoA Reductase Inhibitors (Statins)					
Rosuvastatin calcium (Crestor and generics)	5 mg 10 mg 20 mg 40 mg	tab	0.2311 0.2437 0.3046 0.3582	10 mg to 40 mg daily	89 to 131
Atorvastatin calcium (Lipitor and generics)	10 mg 20 mg 40 mg 80 mg	tab	0.3138 0.3922 0.4216 0.4216	10 mg to 80 mg at bedtime	115 to 154
Fluvastatin sodium (Lescol and generics)	20 mg 40 mg	cap	0.2202 0.3092	20 mg to 40 mg at bedtime	80 to 113
Fluvastatin sodium (Lescol XL)	80 mg	tab	1.5514	80 mg daily	566
Lovastatin (Mevacor and generics)	20 mg 40 mg	tab	0.4919 0.8985	20 mg to 80 mg at bedtime	180 to 656
Pravastatin sodium (Pravachol and generics)	10 mg 20 mg 40 mg	tab	0.4050 0.4778 0.5755	10 mg to 40 mg at bedtime	148 to 210
Simvastatin (Zocor and generics)	5 mg 10 mg 20 mg 40 mg 80 mg	tab	0.1841 0.3642 0.4501 0.4501 0.4501	10 mg to 80 mg at bedtime	133 to 164
Cholesterol Absorption Inhibitor					
Ezetimibe (Ezetrol)	10 mg	tab	0.3260	10 mg daily	119

cap = capsule; PCSK0 = proprotein convertase subtilisin/kexin type 9; SC = subcutaneous; tab = tablet.
[a] Source: Manufacturer's submitted market price.[1]
[b] Source: IMS Brogan DeltaPA.[24]
[c] Based on whether 140 mg is administered every two weeks or 420 mg once monthly, the latter calculated as three 140 mg doses per month.
Source: Ontario Drug Benefit Formulary, accessed April 2016, unless otherwise stated.[23]

TABLE 5: COST COMPARISON TABLE FOR OTHER TREATMENTS USED FOR THE TREATMENT OF PRIMARY HYPERLIPIDEMIA OR MIXED DYSLIPIDEMIA

Drug / Comparator	Strength	Dosage Form	Price ($)	Dosage	Annual Cost ($)
Fibrates					
Fenofibrate (Lipidil EZ)	48 mg 145 mg	tab	0.3560 0.9113	48 mg to 145 mg daily	130 to 333
Bezafibrate (Bezalip and generics)	400 mg	tab	2.2170	400 mg every morning or at bedtime	809
Micro-coated fenofibrate (Lipidil Supra and generics)	160 mg	tab	0.3116	160 mg daily	114
Fenofibrate (Lipidil and generics)	100 mg	cap	0.6105	3 to 4 caps divided three times daily before meals	669 to 891
Fenofibrate (Lipidil Micro and generics)	67 mg 200 mg	Cap	0.4714[a] 0.2723	67 mg to 200 mg daily	99 to 172
Gemfibrozil (Lopid and generics)	300 mg	cap	0.1340	600 mg twice daily after food	49
Binders/Bile Acid Sequestrants					
Colesevelam (Lodalis)	625 mg	tab	1.1154	2.5 g to 4.5 g daily	1,628 to 2,850
Cholestyramine resin (Questran, Olestyr, and generics)	4 g/packet	oral powder	1.3167	one packet 1 to 6 times daily	481 to 2,884
Colestipol HCl: - Colestid Regular - Colestid Orange	 5 g/packet 7.5 g/ packet	oral powder	 0.9550 0.9550	1 to 6 packets in divided doses daily	349 to 2,091

cap = capsule; tab = tablet.
[a] Source: Newfoundland and Labrador Interchangeable Drug Products Formulary April 2016.[25]
Source: Ontario Drug Benefit Formulary, accessed April 2016, unless otherwise stated.[23]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 6: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS ALIROCUMAB + MTS RELATIVE TO MTS ALONE?

Alirocumab + MTS vs. MTS Alone	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$170,478 per QALY $141,960 per life-year					

CE = cost-effectiveness; MTS = maximally tolerated statin therapy; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.
Based on CADTH Common Drug Review (CDR) best estimate.

APPENDIX 3: ADDITIONAL INFORMATION

FIGURE 2: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments *Reviewer to provide comments if checking "no"*			
Was the material included (content) sufficient?		X	
Comments *Reviewer to provide comments if checking "poor"*			
Was the submission well organized and was information easy to locate?	X		
Comments *Reviewer to provide comments if checking "poor"*			

FIGURE 3: AUTHORS' INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to CDR
☐ Adaptation of Global model/Canadian model done by the manufacturer
☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis			X

CDR = CADTH Common Drug Review.

APPENDIX 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF ALIROCUMAB

TABLE 7: SUMMARY OF THE NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE) REVIEW OF ALIROCUMAB

	NICE Review
Date	Draft appraisal published January 2016.[26] Final guidance expected June 2016.
Drug	Alirocumab; a single-use, pre-filled auto-injector pen, 75 mg and 150 mg doses
Reported Price	A confidential patient access scheme was agreed with the Department of Health. Without the patient access scheme, a pen of alirocumab 75 mg and 150 mg costs £168.
Treatment	Dose frequency: 1 injection (75 mg or 150 mg) every 2 weeks
Comparators	HeFH population: alirocumab + statins + ezetimibe vs. statins + ezetimibe High CV risk population: alirocumab + statins vs. statins High CV population who cannot tolerate statins: alirocumab + ezetimibe vs. ezetimibe
Population Modelled	• Patients with HeFH for primary prevention • Patients with HeFH for secondary prevention • Patients with non-familial hypercholesterolemia with existing high-risk CV disease, coronary revascularization, or other arterial revascularization procedures • Patients with non-familial hypercholesterolemia, recurrent CV events, or polyvascular disease
Time Horizon	Lifetime
Cycle Length	1 year
Discount Rate	3.5% on both costs and outcomes
Type of Model	• Cost-utility analysis: Manufacturer constructed a Markov model to assess adjunctive alirocumab in patients with hypercholesterolemia (at high risk of CV events) who failed to reach LDL-C target of 1.81 mmol/L with MTS (± other LLTs) or in patients who are statin intolerant or for whom statin is contraindicated. • Model simulates occurrence of CV events for a single cohort of patients (e.g., HeFH primary prevention and secondary prevention) or for mixed cohort (e.g., high-risk CVD). • Model allows annual transitions from one health state to another based on predicted risks of CV events (fatal and non-fatal) and risk of death from non-CV causes.
Key Outcomes	QALYs; life-years; costs
Manufacturer Results	• HeFH primary prevention: ○ £36,793 per QALY for alirocumab + statin + ezetimibe vs. statin + ezetimibe ○ £16,896 per QALY for alirocumab + statin vs. ezetimibe + statin • For the HeFH secondary prevention population: ○ £16,896 per QALY for alirocumab + statin + ezetimibe vs. statin + ezetimibe ○ £20,352 per QALY for alirocumab + statin vs. ezetimibe + statin • For the high-risk CV disease population (including statin intolerant patients): ○ £19,751 per QALY for alirocumab + statin vs. statin alone ○ £24,175 per QALY for alirocumab + statin vs. ezetimibe + statin ○ £17,256 per QALY for alirocumab + ezetimibe vs. ezetimibe alone in statin intolerant ○ £17,295 per QALY for alirocumab alone vs. ezetimibe alone in statin intolerant • For the recurrent events/polyvascular disease population (including statin intolerant patients): ○ £19,447 per QALY for alirocumab + statin vs. statin alone ○ £23,078 per QALY for alirocumab + statin vs. ezetimibe + statin ○ £13,669 per QALY for alirocumab + ezetimibe vs. ezetimibe alone in statin intolerant ○ £13,469 per QALY for alirocumab alone vs. ezetimibe alone in statin intolerant
Sources of Uncertainty	• Alirocumab modelled through reductions in LDL-C linked with reductions in CV event rates using a published meta-analysis of phase II and III trials

	NICE Review
	• Lack of relevance of LDL-C threshold for population with high-risk CVD (≥ 3.36 mmol/L) • Uncertainty of mean LDL-C levels above specified LDL-C thresholds for specified patient populations • Uncertainty surrounding baseline CV event risks for the HeFH populations
HTA Agency Results	• Modest changes in ICERs for all comparisons in all populations using Navarese meta-analysis to estimate relationship between LDL-C and CV events vs. company's base-case results • Substantially increased ICERs for all comparisons in all populations using CTTC meta-analysis to estimate relationship between LDL-C and CV events vs. company's base-case results
Recommendation	• Draft appraisal document available at this time; final NICE guidance expected in June 2016.
CDR Assessment	The economic evaluations appear to be similar; NICE identified broadly similar limitations to CDR.

CDR = CADTH Common Drug Review; CV = cardiovascular; CVD = cardiovascular disease; CTTC = Cholesterol Treatment Trialists' Collaboration; HeFH = heterozygous familial hypercholesterolemia; HTA = Health Technology Assessment; ICER = incremental cost-effectiveness ratio; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; MTS = maximally tolerated statin therapy; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life-year; vs. = versus.

APPENDIX 5: REVIEWER WORKSHEETS

The following table provides details on the composition of the subgroups considered by the manufacturer.

TABLE 8: MODEL COHORT COMPOSITION

Subgroup	Description	% Mixed Population	Average LDL-C	Minimum LDL-C to Initiate Treatment	% with Diabetes	ODYSSEY Trials Used for Efficacy
HeFH — secondary prevention	Patients with HeFH and a previous CV event	[redacted]	[redacted]	[redacted]	[redacted]	FH 1 and FH 2,[20] LONG TERM[27] (HeFH patients), and HIGH FH[28]
ACS: 0 to 12 months	MI or unstable angina with hospitalization during past 0 to 12 months Following an ACS, the risk of CV event recurrence is highest in the first year post-event, slightly lower in the second year post-event and decreases again for subsequent years.	[redacted]	[redacted]	[redacted]	[redacted]	FH 1 and FH 2,[20] COMBO 1,[29] and LONG TERM[27]
Ischemic stroke	History of ischemic stroke Unlike in the case of ACS, the risk of CV events following an ischemic stroke remains relatively constant over time.	[redacted]	[redacted]	[redacted]	[redacted]	FH 1 and FH 2,[20] COMBO 1,[29] and LONG TERM[27]
ACS (13 to 24 months)	MI or unstable angina with hospitalization during past 13 to 24 months Following an ACS, the risk of CV event recurrence still remains high in the second year post-event and decreases in subsequent years.	[redacted]	[redacted]	[redacted]	[redacted]	FH 1 and FH 2,[20] COMBO 1,[29] and LONG TERM[27]
Other CHD	MI or unstable angina ≥ 24 months ago or other evidence of CHD such as a history of stable angina, coronary revascularization, or ischemic heart disease.	[redacted]	[redacted]	[redacted]	[redacted]	FH 1 and FH 2,[20] COMBO 1,[29] and LONG TERM[27]
HeFH (primary prevention)	Patients with HeFH who have not experienced a CV event.	[redacted]	[redacted]	[redacted]	[redacted]	FH 1 and FH 2,[20] LONG TERM[27] (HeFH patients), and HIGH FH[28]

ACS = acute coronary syndrome; CHD = coronary heart disease; CV = cardiovascular; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction.

TABLE 9: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Treatment-specific reductions in LDL-C were derived from the ODYSSEY clinical trials program. Efficacy in HeFH patients was informed by the ODYSSEY FH 1, FH 2, LONG TERM, and HIGH FH trials while efficacy in high-risk CV patients was based on ODYSSEY FH 1, FH 2, COMBO 1, and LONG TERM. When ezetimibe is considered as a comparator, efficacy is informed by the COMBO 2, OPTIONS 1, and OPTIONS 2 trials.	The use of the FH trials to inform efficacy among non-HeFH patients may be assessed as questionable.
Natural History	Patient cohort composition and characteristics were derived from the UK THIN database.[6] Starting age was based on a study of statin users in Canada,[7] proportion of males and females was based on UK THIN, and descriptive CV risk was based on observed events in the UK THIN cohort. LDL-C lowering was linked to reduced risk of CV events through use of Navarese et al.'s meta-analysis[4] for alirocumab + MTS patients and the 2012 CTTC meta-analysis[5] for MTS alone patients.	Use of UK THIN database and cohort composition was felt to be acceptable and representative by clinical expert. The use of different values linking LDL-C to CV risk is problematic and serves to bias results in favour of alirocumab. Further, methodological problems have been noted in Navarese et al.'s study.[17,18]
Utilities	Baseline utilities were based on a pooled analysis of EQ-5D estimates from the pooled ODYSSEY trials (FH 1, FH 2,[20] HIGH FH,[28] COMBO 1,[29] COMBO 2,[31] and LONG TERM[27] studies) using the Canadian time trade-off algorithm. Acute CV event health state disutilities and post-event utilities were applied multiplicatively to state utilities and were informed by values used by NICE in their lipid modification guidelines.[12] Patients would experience acute disutility in the year after their event, after which they would experience a chronic post-event utility.	Given heterogeneity in patient baseline characteristics across trials, the use of utility values from pooling these trials is associated with some uncertainty.
Drugs' Adverse Events	Rates of adverse events were found to be similar between the modelled two groups in the clinical trials and therefore were not considered in the model.	Appropriate
Mortality	Rates of CV death were from observed deaths in UK THIN. Rates of non-CV mortality were based on age-stratified and sex-stratified values from Statistics Canada.	Appropriate
Costs		
Drug	Praluent: manufacturer's submitted cost, adjusted for compliance MTS: weighted average costs of atorvastatin, rosuvastatin, and simvastatin from ODB formulary[23] in proportion seen in ODYSSEY trials, adjusted for compliance based on Rx Dynamics data obtained by the manufacturer.[2]	Appropriate. Compliance rates of 98% for alirocumab were noted to be high by the clinical expert.
Event	Costs of revascularization, non-fatal ACS, and non-fatal MI were derived from CADTH publications that estimated these costs, which include acute care costs and treatment costs.[13-15]	Appropriate
Death	The costs of CV death were considered based on economic evaluations by Anis et al.[16] and CADTH,[15] which estimated the costs of fatal MI and IS. These costs comprise acute care costs and treatment costs. Deaths from other causes were not costed.	Suspected source of double counting with the costs of non-fatal CV events

ACS = acute coronary syndrome; CTTC = Cholesterol Treatment Trialists' Collaboration; CV = cardiovascular; EQ-5D = EuroQoL 5-Dimensions; HeFH = heterozygous familial hypercholesterolemia; IS = ischemic stroke; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; MTS = maximally tolerated statin therapy; NICE = National Institute for Health and Care Excellence; ODB = Ontario Drug Benefit; THIN = The Health Improvement Network (UK).

TABLE 10: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Treatment-specific reductions in LDL-C were assumed to be constant over the time of the duration of clinical trials, and then maintained over the rest of the time horizon.	Unclear whether appropriate, although CDR acknowledges paucity of long-term data
Patients were assumed to discontinue therapy according to the rates observed from the pooled ODYSSEY trials; further, discontinuation was assumed to apply at a constant rate over the entire treatment duration of the model.	Discontinuation rates were judged to be higher than would be seen in practice by the CDR clinical expert. Nevertheless, the model is not sensitive to varying this data.
Composition of MTS reflected composition in clinical practice.	Appropriate
Composition of cohort reflected the reimbursement request population.	Appropriate
Alirocumab compliance (98%) reflected compliance that would be seen in clinical practice.	Unclear whether appropriate, however the consulting clinical expert questioned whether it would be as high in practice. The model is not sensitive to varying this data.
UK THIN population reflected Canadian population.	Plausible
MTS is most relevant comparator.	Appropriate: Other potential comparators included MTS + EZE or evolocumab. The under-prioritization of MTS + EZE was based on the low prevalence of EZE use in Canada (6% of all prescribed LLTs in 2014 were EZE as per IMS Brogan data cited in the pharmacoeconomic submission).[2] While evolocumab received a positive reimbursement recommendation from CDEC,[8] it is not reimbursed by any formularies at the time of writing and there is no comparative efficacy data with alirocumab.
Decrease in CV events due to LDL-C reduction was immediate for a treated patient.	Unclear whether appropriate
Subgroup-specific baseline utilities were applied as a constant throughout the analysis.	Uncertain

CDEC = CADTH Canadian Drug Expert Committee; CDR = CADTH Common Drug Review; CV = cardiovascular; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; MTS = maximally tolerated statin therapy; THIN = The Health Improvement Network (UK).

Manufacturer's Results

Table 10 presents the details of the manufacturer results for the primary mixed population assessed by the model and by subgroup.

TABLE 11: DETAILED MANUFACTURER RESULTS

Patient Group	Total Cost ($) ALI	Total Cost ($) MTS	Inc. Cost ($)	QALY ALI	QALY MTS	Inc. QALY	ICUR ($/QALY)	LY ALI	LY MTS	Inc. LY	ICER ($/LY)
Mixed population	48,864	16,342	32,522	8.40	7.69	0.70	**46,416**	9.86	9.15	0.71	**46,111**
HeFH	48,790	15,073	33,718	9.54	8.98	0.56	**60,543**	10.54	10.01	0.53	**63,851**
HeFH – primary	45,359	10,059	35,300	10.11	9.70	0.42	**84,875**	10.91	10.53	0.39	**91,260**
HeFH – secondary	57,483	27,923	29,560	8.04	7.08	0.96	**30,888**	9.51	8.57	0.94	**31,519**
High-risk CV patients	48,872	16,483	32,389	8.27	7.55	0.72	**45,189**	9.78	9.06	0.73	**44,668**
ACS (0 to 12 months)	49,285	18,109	31,176	8.25	7.44	0.81	**38,575**	9.68	8.88	0.80	**39,013**
History of IS	49,004	17,173	31,831	7.36	6.65	0.71	**44,663**	9.25	8.49	0.76	**42,071**
ACS (13 to 24 months)	48,525	15,991	32,534	8.36	7.68	0.68	**47,761**	9.76	9.08	0.68	**47,587**
Other CHD	47,439	13,823	33,616	8.66	8.09	0.57	**58,845**	10.06	9.49	0.57	**58,808**

ACS = acute coronary syndrome; ALI = alirocumab; CHD = coronary heart disease; CV = cardiovascular; HeFH = heterozygous familial hypercholesterolemia; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; Inc. = incremental; IS = ischemic stroke; LY = life-year; MTS = maximally tolerated statin therapy; QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission.[2]

Additional Manufacturer Sensitivity Analyses

The manufacturer also reported sensitivity analyses comparing alirocumab with ezetimibe (EZE) (without maximally tolerated statin [MTS] therapy) and with EZE + MTS, reporting incremental cost-utility ratios (ICURs) of $59,867 and $66,169, respectively.

The manufacturer's results for the comparison of alirocumab + MTS versus EZE + MTS for the full mixed population and by patient subgroup are presented in Table 12. This comparison was judged to be of limited interest compared to the comparison of alirocumab + MTS versus MTS alone given that EZE use remains low in Canada (accounting for 6% of all lipid-lowering therapies sold in 2014).[2] Results from a cost-effectiveness assessment using MTS + EZE as a comparator are similar to those using MTS alone.

TABLE 12: MANUFACTURER RESULTS, ALIROCUMAB + MTS VERSUS EZETIMIBE + MTS

Patient Group	Total Cost ($) ALI	Total Cost ($) MTS	Inc. Cost ($)	QALY ALI	QALY MTS	Inc. QALY	ICUR ($/QALY)	LY ALI	LY MTS	Inc. LY	ICER ($/LY)
Mixed population	48,856	15,922	32,934	8.40	7.90	0.50	**66,169**	9.86	9.36	0.50	66,058
HeFH	48,783	14,697	34,086	9.54	9.15	0.39	**87,990**	10.55	10.18	0.36	93,542
HeFH – primary	57,470	26,672	30,798	8.04	7.38	0.66	**46,364**	9.51	8.87	0.64	47,831
HeFH – secondary	45,353	10,018	35,335	10.11	9.82	0.29	**122,184**	10.92	10.65	0.27	131,797
High-risk CV patients	48,865	16,059	32,806	8.27	7.76	0.51	**64,318**	9.79	9.27	0.51	63,884
ACS (0 to 12 months)	49,271	17,439	31,832	8.25	7.67	0.58	**54,802**	9.68	9.11	0.57	55,731
History of IS	48,996	16,872	32,124	7.36	6.85	0.52	**62,108**	9.26	8.71	0.55	58,800
ACS (13 to 24 months)	48,514	15,660	32,855	8.37	7.88	0.49	**67,006**	9.77	9.28	0.49	67,066
Other CHD	47,431	13,673	33,758	8.66	8.25	0.51	**82,231**	10.06	9.65	0.41	82,493

ACS = acute coronary syndrome; ALI = alirocumab; CHD = coronary heart disease; CV = cardiovascular; HeFH = heterozygous familial hypercholesterolemia; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; Inc. = incremental; IS = ischemic stroke; LY = life-year; MTS = maximally tolerated statin therapy; QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission.[2]

CADTH Common Drug Review Reanalyses

To account for the limitations identified above, CADTH Common Drug Review (CDR) undertook the following analyses:

1. **Use of Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis to link low-density lipoprotein cholesterol (LDL-C) reductions and CV outcomes**
   The CTTC meta-analysis was used in both the alirocumab + MTS and MTS alone groups to account for the initial use of two different meta-analyses.
2. **Corrected LDL-C cut-off values**
   Minimum LDL-C cut-offs for treatment initiation were changed to reflect risk-group appropriate values for heterozygous familial hypercholesterolemia (HeFH) secondary prevention patients (changed from 2.6 mmol/L to 1.8 mmol/L, reflecting very-high-risk patients) and high-risk CV patients with other coronary heart disease (CHD) (changed from 3.4 mmol/L to 2.6 mmol/L, reflecting high-risk patients) based on Canadian Cardiovascular Society guidelines[21] and the European Atherosclerosis Society's consensus statement on familial hypercholesterolemia[21] and confirmed in the published ODYSSEY FH 1 and FH 2 studies.[20]
3. **Reduction of the cost of CV death**
   The cost of CV deaths was reduced by 50%.
4. **20-year horizon**
   A 20-year time horizon was considered to rectify uncertainty in long-term efficacy estimates.

TABLE 13: CDR REANALYSES BY IDENTIFIED LIMITATION — MIXED POPULATION

Patient Group	Total Cost ($) ALI	Total Cost ($) MTS	Inc. Cost ($)	QALY ALI	QALY MTS	Inc QALY	ICUR ($/QALY)	LY ALI	LY MTS	Inc. LY	ICER ($/LY)
Mfr.'s base case	*48,864*	*16,342*	*32,522*	*8.40*	*7.69*	*0.70*	***46,416***	*9.86*	*9.15*	*0.71*	*46,111*
CTTC meta-analysis	48,733	16,342	32,392	8.03	7.69	0.34	**95,706**	9.46	9.15	0.31	104,447
LDL-C cut-off values	47,972	14,840	33,132	8.47	7.85	0.61	**54,203**	9.92	9.30	0.62	53,735
Costs of death reduced by 50%	47,585	14,748	32,837	8.40	7.69	0.70	**46,865**	9.86	9.15	0.71	46,557
20-year horizon	47,432	15,207	32,225	8.11	7.46	0.65	**49,734**	9.49	8.85	0.64	50,235
CDR best estimate	45,357	12,379	32,978	7.86	7.60	0.26	**126,375**	9.21	8.97	0.23	141,424

ALI = alirocumab; CDR = CADTH Common Drug Review; CTTC = Cholesterol Treatment Trialists' Collaboration; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; Inc. = incremental; LDL-C = low-density lipoprotein cholesterol; LY = life-year; Mfr. = manufacturer; MTS = maximally tolerated statin therapy; QALY = quality-adjusted life-year.

TABLE 14: CDR BEST ESTIMATES (ADDRESSING ALL LIMITATIONS) BY SUBGROUP

Patient Group	Total Cost ($) ALI	Total Cost ($) MTS	Inc. Cost ($)	QALY ALI	QALY MTS	Inc. QALY	ICUR ($/QALY)	LY ALI	LY MTS	Inc. LY	ICER ($/LY)
Mixed population	45,357	12,379	32,978	7.86	7.60	0.26	**126,375**	9.21	8.97	0.23	141,424
HeFH[a]	46,014	11,996	34,019	8.88	8.64	0.24	**143,401**	9.80	9.60	0.20	173,100
HeFH – primary	43,361	8,072	35,289	9.39	9.20	0.19	**190,006**	10.12	9.97	0.15	229,478
HeFH – secondary	54,393	25,059	29,333	7.41	6.93	0.49	**60,092**	8.79	8.36	0.42	69,458
High-risk CV patients*	45,283	12,422	32,861	7.74	7.48	0.26	**124,664**	9.14	8.90	0.24	138,493
ACS (0 to 12 months)	46,537	15,483	31,054	7.59	7.23	0.36	**86,005**	8.92	8.60	0.31	98,616
History of IS	46,034	14,479	31,554	6.80	6.50	0.30	**106,726**	8.56	8.29	0.28	114,084
ACS (13 to 24 months)	45,764	13,435	32,329	7.75	7.46	0.30	**109,573**	9.05	8.79	0.26	122,949
Other CHD	44,892	11,408	33,484	8.05	7.81	0.24	**138,310**	9.35	9.13	0.22	155,130

ACS = acute coronary syndrome; ALI = alirocumab; CDR = CADTH Common Drug Review; CHD = coronary heart disease; CV = cardiovascular; HeFH = heterozygous familial hypercholesterolemia; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; Inc. = incremental; IS = ischemic stroke; LY = life-year; MTS = maximally tolerated statin therapy; QALY = quality-adjusted life-year.

[a] For all HeFH patients, the proportions of primary and secondary HeFH were assumed to be the same differential proportion of these used for the base case (mixed population). The same was assumed for high-risk CV patients' subpopulations.

TABLE 15: CDR RESULTS (ADDRESSING ALL LIMITATIONS) FOR ALIROCUMAB + MTS VERSUS EZETIMIBE + MTS FOR THE FULL MIXED COHORT AND BY SUBGROUP

Patient Group	Total Cost ($) ALI	Total Cost ($) MTS	Inc. Cost ($)	QALY ALI	QALY MTS	Inc. QALY	ICUR ($/QALY)	LY ALI	LY MTS	Inc. LY	ICER ($/LY)
Mixed population	45,347	11,960	33,387	7.86	7.72	0.14	**238,542**	9.21	9.08	0.13	264,909
HeFH*	46,006	11,491	34,515	8.88	8.76	0.12	**279,496**	9.80	9.70	0.10	334,177
HeFH – primary	43,355	7,900	35,455	9.39	9.29	0.10	**370,524**	10.12	10.04	0.08	442,505
HeFH – secondary	54,379	23,066	31,313	7.42	7.16	0.25	**123,439**	8.79	8.57	0.22	142,022
High-risk CV patients[a]	45,273	12,012	33,261	7.74	7.60	0.14	**234,557**	9.14	9.01	0.13	258,692
ACS (0 to 12 months)	46,522	14,463	32,058	7.59	7.40	0.19	**164,810**	8.92	8.75	0.17	188,844
History of IS	46,024	14,001	32,023	6.80	6.64	0.16	**198,907**	8.57	8.41	0.15	211,095
ACS (13 to 24 months)	45,753	12,856	32,897	7.75	7.60	0.16	**208,014**	9.05	8.91	0.14	231,818
Other CHD	44,883	11,091	33,792	8.06	7.93	0.13	**260,454**	9.35	9.23	0.12	290,056

ACS = acute coronary syndrome; ALI = alirocumab; CDR = CADTH Common Drug Review; CHD = coronary heart disease; CV = cardiovascular; HeFH = heterozygous familial hypercholesterolemia; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; Inc. = incremental; IS = ischemic stroke; LY = life-year; MTS = maximally tolerated statin therapy; QALY = quality-adjusted life-year.

[a] For all HeFH patients, the proportions of primary and secondary HeFH were assumed to be the same differential proportion of these used for the base case (mixed population). The same was assumed for high-risk CV patients' subpopulations.

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