Common Drug Review
Pharmacoeconomic Review Report

February 2016

Drug	Evolocumab (Repatha)
Indication	1. As an adjunct to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). 2. As an adjunct to diet and other LDL-lowering therapies (eg, statins, ezetimibe, LDL apheresis) in adult patients and adolescent patients aged 12 years and over with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.
Listing request	3. High-risk patients with primary hyperlipidemia or mixed dyslipidemia who have experienced a prior cardiovascular event and who cannot reach the LDL-C target with standard of care. 4. Heterozygous familial hypercholesterolemia patients who are not at the LDL-C target with standard of care.
Dosage Form	140 mg/mL Pre-filled auto-injector/pre-filled syringe
NOC Date	Sept. 10 2015
Manufacturer	Amgen Canada Inc.

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

TABLE OF CONTENTS

Tables

Figure

ABBREVIATIONS

ACS	acute coronary syndrome
AE	adverse event
AI	auto-injector
CADTH	Canadian Agency for Drugs And Technologies in Health
CDR	CADTH Common Drug Review
CHD	coronary heart disease
CV	cardiovascular
CVD	cardiovascular disease
HeFH	heterozygous familial hypercholesterolemia
ICUR	incremental cost-utility ratio
IS	ischemic stroke
LDL	low-density–lipoprotein
PCSK9	proprotein convertase subtilisin/kexin type 9
QALY	quality-adjusted life-year
SC	subcutaneous
SI	statin intolerance

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Evolocumab 140 mg/mL
Study Question	To perform an economic evaluation of evolocumab from a Canadian publicly funded provincial payer perspective in: 1. patients with non-familial primary hyperlipidemia and/or mixed dyslipidemia 2. high-risk patients[a] with non-familial primary hyperlipidemia and/or mixed dyslipidemia who have experienced a CV event and who cannot reach the LDL-C target with standard of care 3. patients with HeFH who cannot reach the LDL-C target with standard of care 4. SI patients with non-familial primary hyperlipidemia and/or mixed dyslipidemia who cannot reach the LDL-C target with standard of care
Type of Economic Evaluation	Cost-utility analysis
Target Population	• All patients with non-familial primary hyperlipidemia and/or mixed dyslipidemia • High-risk patients[a] with non-familial primary hyperlipidemia and/or mixed dyslipidemia • Patients with HeFH • Patients who are SI
Treatment	Evolocumab 140 mg administered subcutaneously every two weeks either as monotherapy or in combination with medium- or high-intensity statins
Outcome	QALYs
Comparators	1. Ezetimibe plus medium- or high-intensity statins or medium- or high-intensity statins alone 2. Ezetimibe plus medium- or high-intensity statins or medium- or high-intensity statins alone 3. Ezetimibe plus high-intensity statins or high-intensity statins alone 4. Ezetimibe or no treatment
Perspective	Publicly funded health care system
Time Horizon	Lifetime horizon (up to the age of 120 years)
Results for Base Case	1. Evolocumab + medium- or high-intensity statins[b] vs. • Medium- or high- intensity statins alone: $100,482 per QALY • Ezetimibe plus medium- or high- intensity statins: $151,112 per QALY 2. Evolocumab + medium- or high-intensity statins vs. • Medium- or high- intensity statins alone: $79,598 per QALY • Ezetimibe plus medium- or high- intensity statins: $115,284 per QALY 3. Evolocumab + high-intensity statins vs. • High-intensity statins alone: $18,457 per QALY • Ezetimibe plus high-intensity statins: $34,744 per QALY 4. Evolocumab alone vs. • No treatment: $57,943 per QALY • Ezetimibe: $105,548 per QALY
Key Limitations	CDR noted the following limitations with the manufacturer's submission: • The efficacy of ezetimibe in lowering LDL-C in HeFH patients was derived from a clinical trial that did not include background statin therapy in the design. The true efficacy of ezetimibe plus background statin therapy in HeFH patients is underestimated; the impact of this limitation biased the results in favour of evolocumab. • Treatment effects of LDL-C lowering on CHD event risk were derived from patient populations on less intensive statin therapy; this is not consistent with the

	increased intensity statin therapy observed in the patient populations in the clinical trials for evolocumab (LAPLACE-2 and RUTHERFORD-2). The included rate ratios for CHD thus biased the results in all base-case analyses in favour of evolocumab. • Model time horizon and treatment duration were considered too long, based on the patient starting age of 59 years and clinical prognosis for patients with familial and non-familial hyperlipidemia. • Health state utilities were based on an industry-funded study that was conducted in the UK, despite availability of Canadian studies with utility data for CV events. • Estimation of the annual costs of statin therapy was not consistent with publicly available costs of statin therapy in Canada.
CDR Estimates	CDR performed a number of reanalyses. Results were sensitive to LDL-C effect on CHD death, ezetimibe efficacy on lowering LDL-C, and time horizon, resulting in a wide range of ICURs. When using adjusted values for LDL-C effect on CHD death and for ezetimibe efficacy on LDL-C, and assuming a shorter time horizon of 20 years: 1. Evolocumab + medium- or high-intensity statins vs. • Medium- or high- intensity statins alone: $180,427 per QALY • Ezetimibe plus medium- or high-intensity statins: $397,180 per QALY 2. Evolocumab + medium- or high-intensity statins vs. • Medium- or high- intensity statins alone: $124,922 per QALY • Ezetimibe plus medium- or high-intensity statins: $263,929 per QALY 3. Evolocumab + high-intensity statins vs. • High-intensity statins alone: $23,822 per QALY • Ezetimibe plus high-intensity statins: $68,813 per QALY 4. Evolocumab alone vs. • No treatment: $95,842 per QALY • Ezetimibe: $172,177 per QALY

CDR = CADTH Common Drug Review; CHD = coronary heart disease; CV = cardiovascular; HeFH = heterozygous familial hypercholesterolemia; ICUR = incremental cost-utility ratio; LDL-C = low-density–lipoprotein cholesterol; QALY = quality-adjusted life-years; SI = statin-intolerant; vs. = versus.

[a] High-risk patients are characterized per the Canadian Cardiovascular Society (CCS) guidelines definition (e.g., patients with prior CV disease, an adjusted Framingham Risk Score ≥ 20%, age ≥ 40 years with diabetes, high-risk hypertension, or high-risk kidney disease).[1,2]

[b] Medium-intensity statin therapy was defined as rosuvastatin 10 mg daily; high-intensity statin therapy was defined as atorvastatin 20 mg daily.[1]

EXECUTIVE SUMMARY

Background

Evolocumab is a fully human monoclonal antibody that binds to human proprotein convertase subtilisin/kexin type9 (PCSK9). Evolocumab is indicated as an adjunct to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low-density–lipoprotein (LDL) cholesterol.[3]

The recommended dose of evolocumab for primary hyperlipidemia is either 140 mg every two weeks or 420 mg once monthly administered by subcutaneous (SC) injection; both doses are clinically equivalent.[3] One pre-filled syringe or pre-filled auto-injector (AI) delivers the 140 mg dose every two weeks, and three pre-filled syringes or three pre-filled AIs administered consecutively within 30 minutes deliver the 420 mg dose once monthly.[3] The manufacturer submitted a confidential price of $[redacted] per 140 mg/mL single-use pre-filled syringe ($[redacted] daily) or single-use pre-filled auto-injector. Based on the product monograph, the pre-filled syringes are not available in Canada.

The manufacturer is requesting listing in the following subgroups:

- high-risk patients with primary hyperlipidemia or mixed dyslipidemia who have experienced a prior cardiovascular (CV) event and who cannot reach the LDL cholesterol target with standard of care
- HeFH patients who are not at the LDL cholesterol target with standard of care.

The manufacturer defined high-risk patients with non-familial primary hyperlipidemia and/or mixed dyslipidemia as patients who have experienced a CV event per the Canadian Cardiovascular Society guidelines definition (e.g., Framingham Risk Score ≥ 20%),[2] while all HeFH patients were considered high-risk patients by the manufacturer.[4]

The manufacturer submitted a cost-utility analysis of evolocumab either as add-on to medium- or high-intensity statins in patients with primary hyperlipidemia and/or mixed dyslipidemia, high-risk patients with non-familial hyperlipidemia with a prior CV event compared with medium- or high-intensity statins alone or in combination with ezetimibe. The manufacturer defined medium-intensity statin therapy as rosuvastatin 10 mg daily and high-intensity statin as atorvastatin 20 mg daily. The manufacturer also assessed the cost utility of evolocumab as add-on to high-intensity statins in patients with HeFH. The treatment effects were assessed by combining the treatment efficacy in terms of absolute LDL cholesterol lowering from the evolocumab trials (LAPLACE-2 and RUTHERFORD-2)[5,6] and from a meta-analysis of 26 randomized clinical trials of statins that estimated the effect of absolute LDL cholesterol lowering on CV event outcomes (Baigent et al.).[7] The analyses were conducted from the perspective of a Canadian publicly funded health care system assuming a lifelong time horizon (up to patient age of 120).[1]

The manufacturer also provided an analysis of evolocumab used as monotherapy in statin-intolerant patients. However, as evolocumab is only indicated as add-on to diet and statin therapy, the results of the analysis as monotherapy in statin-intolerant patients will not be reported in this review.

In all analyses, the manufacturer reported that treatment with evolocumab resulted in improved quality-adjusted life-years (QALYs) at incremental costs when compared with the treatments selected by the manufacturer. The incremental cost-utility ratios (ICURs) for evolocumab were more than $57,000 per

QALY across all populations and subgroups, except in patients with HeFH, in which ICURs ranged from $18,457 to $34,744 per QALY.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several limitations of the submitted economic analysis. Key limitations were that the results were sensitive to the efficacy of ezetimibe when added to background statin therapy in lowering LDL cholesterol in patients with hyperlipidemia (both primary hyperlipidemia and with prior CV events) and in patients with HeFH; the results were also sensitive to the impact of LDL cholesterol lowering in reducing the risk of death due to coronary heart disease (CHD); and the model time horizon was not reflective of clinical practice and life expectancy. Other limitations included the uncertainty in the health state utility values and the estimation of annual costs associated with background statin therapy. CDR considered alternative efficacy for ezetimibe when added to background statin therapy in patients with primary hyperlipidemia, in high-risk patients with hyperlipidemia, and in patients with HeFH. Alternative values were also used for the effect of LDL cholesterol lowering on risk of CHD death. A reduced time horizon more reflective of clinical practice and life expectancy of the population of interest was selected. Annual costs for background statin therapy were also adjusted to reflect current reimbursed unit prices for statins in Canada.

CDR results show that the ICUR for evolocumab plus medium- or high- intensity statins compared with medium- or high- intensity statins alone ranges from $124,922 to $180,427 per QALY in patients with primary hyperlipidemia and high-risk patients with hyperlipidemia. When compared with ezetimibe plus medium- or high- intensity statins, the ICUR for evolocumab plus medium- or high- intensity statins ranges from $263,929 to $397,180 per QALY. In patients with HeFH, evolocumab plus high-intensity statins resulted in an ICUR range from $23,822 to $68,813 per QALY when compared with high-intensity statins alone and ezetimibe plus high-intensity statins. In patients with statin intolerance, evolocumab alone resulted in an ICUR range from $95,842 to $172,177 per QALY when compared with no treatment and ezetimibe.

Conclusions

There are a number of limitations with how the evidence for the comparative clinical effectiveness of evolocumab versus ezetimibe was modelled in the economic analysis. This resulted in uncertainty in the assessments of evolocumab's cost-effectiveness versus ezetimibe in patients with hyperlipidemia and HeFH. In the analyses submitted by the manufacturer, the ICURs for evolocumab were more than $57,000 per QALY across all populations and subgroups, except in patients with HeFH, in which ICURs ranged from $18,457 to $34,744 per QALY when evolocumab was compared with background statin therapy or ezetimibe plus background statin therapy.

CDR reanalyses to address the identified limitations of the manufacturer's economic analysis showed that results were sensitive to ezetimibe efficacy when added to background statin therapy, to the impact of LDL cholesterol lowering on CHD death risk, and to model time horizon and treatment duration across all populations and subgroups except patients with HeFH. The ICURs for evolocumab added on to statins, when compared with ezetimibe plus background statins, were more than $100,000 per QALY, and as high as $397,000 per QALY in some patients subgroups. In patients with HeFH, the ICUR for evolocumab from CDR reanalyses increased by up to $68,813 per QALY.

Based on the limitations identified, for most of the patient populations included in this submission, evolocumab would require a reduction in price of 50% to 80% to be considered a cost-effective option compared with statins alone or ezetimibe plus statins, based on conventionally accepted thresholds.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer-submitted cost-utility analysis evaluating evolocumab added on to medium- or high-intensity statins in adult patients with primary hyperlipidemia (heterozygous familial hypercholesterolemia [HeFH] and non-familial) or mixed dyslipidemia compared with medium- or high-intensity statins alone or in combination with ezetimibe. In patients with HeFH, evolocumab was added to high-intensity statins and was compared with high-intensity statin therapy alone or in combination with ezetimibe. The reference case used a lifetime time horizon (up to a maximum age of 120 years old) using the Canadian public payer perspective.[1]

The submitted model included several acute and post-acute health states including acute coronary syndrome, ischemic stroke, heart failure, and cardiovascular (CV) and non-CV death (Figure 1). The cycle length was set at one year, at the end of which patients could either transition to another health state or remain in their current health state.[1] Baseline CV risk, reflective of the CV risk based on background therapy, was calculated for each population modelled based on published risk equations. For patients with non-familial hyperlipidemia and/or mixed dyslipidemia, the baseline CV risk was based on Framingham risk predictions for a primary CV event (D'Agostino et al.[8]) and the Reduction of Atherothrombosis for Continued Health (REACH) risk prediction engine for recurrent events (Wilson et al.).[9] Baseline CV risk was adjusted for the HeFH population due to that population's increased risk of developing CVD; baseline risk was multiplied by an age-specific risk ratio based on the study of Benn et al.,[10] which pooled odds ratios from patients receiving and not receiving statins in describing the CV event risk for HeFH versus high-risk non-HeFH patients.

Efficacy data for evolocumab in patients with non-familial hyperlipidemia and/or mixed dyslipidemia (primary and secondary prevention) were derived from the LAPLACE-2 study (Robinson et al.).[5] Efficacy for evolocumab in HeFH patients was derived from the RUTHERFORD-2 study (Raal et al.).[6] In a second step, the treatment effects were assessed by combining the treatment efficacy in terms of absolute LDL cholesterol lowering from the evolocumab trial program[5,6,11] and the results of a recent meta-analysis of 26 randomized clinical trials of statins that estimated the effect of absolute LDL cholesterol lowering on CV event outcomes (Baigent et al.).[7]

The baseline utility input was based on Canadian utility data and was set to 0.868 in the model; this utility value was based on utilities reported for the age ranges 40 to 64 and 65 years and older, calculated from a random sample of the Canadian population using the Health Utilities Index instrument (Feeny et al.).[12] The utility for the CV health state was derived from an industry-funded utility study based on a general population sample in the UK in which a total of 200 individuals (55% female, mean age 46.6 years) rated the health states in time trade-off interviews (Matza et al.).[13] The time trade-off utility value for the established cardiovascular disease health state was assumed to be equal to the value attributed to subsequent years of acute coronary syndrome (ACS).[1]

For health state costs, the data source for the acute and long-term cost of unstable angina, myocardial infarction and heart failure were taken from the results of an analysis (Goeree et al.) of Ontario administrative records of 610,000 individuals with diabetes matched with 1,221,704 non-diabetic

individuals.[14] Drug unit costs were derived from the 2015 Ontario Drug Benefit Formulary.[15] Costs were expressed in 2015 Canadian dollars, and the analyses were conducted from the perspective of a Canadian publicly funded health care system, assuming a lifelong time horizon. Probabilistic and univariate sensitivity analyses were conducted to estimate the uncertainty associated with the data. Costs and outcomes beyond one year were discounted at 5%.

2. MANUFACTURER'S BASE CASE

Using a lifetime time horizon (up to the age of 120 years), evolocumab resulted in incremental quality-adjusted life-years (QALYs) and costs, based on patient population and comparator treatments, as follows:

1. Patients with primary hyperlipidemia and/or mixed dyslipidemia: evolocumab plus medium- or high-intensity statins
   - Compared with medium- or high- intensity statins alone, incremental cost-utility ratio (ICUR) of $100,482 per QALY
   - Compared with ezetimibe plus medium- or high-intensity statins, ICUR of $151,112 per QALY
2. High-risk patients with non-familial hyperlipidemia and/or mixed dyslipidemia): evolocumab plus medium- or high- intensity statins
   - Compared with medium- or high- intensity statins alone, ICUR of $79,598 per QALY
   - Compared with ezetimibe plus medium- or high- intensity statins, ICUR of $115,284 per QALY
3. Patients with HeFH: evolocumab plus high-intensity statins
   - Compared with high-intensity statins alone, ICUR of $18,457 per QALY
   - Compared with ezetimibe plus high-intensity statins, ICUR of $34,744 per QALY
4. Patients who are statin-intolerant (SI): evolocumab alone
   - Compared with no treatment, ICUR of $57,943 per QALY
   - Compared with ezetimibe alone, ICUR of $105,351 per QALY

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASES

Base-Case Scenario	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Primary non-familial hyperlipidemia and/or mixed dyslipidemia			
Evolocumab vs. medium- or high-intensity statins alone	49,266	0.49	100,482
Evolocumab vs. ezetimibe plus medium- or high-intensity statins	50,621	0.33	151,112
High-risk patients with primary non-familial hyperlipidemia and/or mixed dyslipidemia			
Evolocumab vs. medium- or high-intensity statins alone	46,650	0.59	79,598
Evolocumab vs. ezetimibe plus medium- or high-intensity statins	47,267	0.41	115,284
Patients with heterozygous familial hyperlipidemia			
Evolocumab vs. high-intensity statins alone	26,767	1.45	18,457
Evolocumab vs. ezetimibe plus high-intensity statins	34,014	0.98	34,744
Patients who are statin-intolerant			
Evolocumab vs. no treatment	40,920	0.71	57,943
Evolocumab vs. ezetimibe alone	45,384	0.43	105,351

QALY = quality-adjusted life-year; vs. = versus.
Source: Adapted from manufacturer's pharmacoeconomic submission, Tables 12 (page 35), 13 (page 39), 14 (page 43), and 15 (page 47).[1]

Please refer to Appendix 4: REVIEWER WORKSHEETS for detailed results.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

Uncertainty in input parameters was explored by the manufacturer through univariate one-way sensitivity analyses conducted using the 95% lower and upper bounds for clinical and utility data while unit costs were varied by +/-20%. The impact of uncertainty due to other model assumptions (e.g., treatment duration, compliance, discount rates) was also assessed. The manufacturer also conducted probabilistic analyses. The results of the manufacturer's sensitivity analyses indicate that the model results are sensitive to the effect of LDL cholesterol lowering on risk of ischemic stroke (IS) in every submitted patient population. In the primary hyperlipidemia analysis, the results were also sensitive to changes in baseline utility, treatment duration, and the effect of LDL cholesterol lowering on risk of IS and death due to coronary heart disease (CHD). In the high-risk patients with hyperlipidemia, the results were also sensitive to treatment duration and effect of LDL cholesterol lowering on IS and CHD death.

The manufacturer performed the probabilistic sensitivity analysis (PSA) by conducting 1,000 Monte Carlo simulations in which values of key parameters were drawn randomly and independently from the parameter distributions. Standard errors were used for the parameter distribution.[16] Beta distributions were used for utilities and estimates for treatment effects on LDL cholesterol, gamma distributions were used for costs, and lognormal distributions were used for the other parameters.[16] The cost-effectiveness acceptability curves (CEACs) indicated that:

- in patients with HeFH, evolocumab had the highest likelihood of being cost-effective (up to 99%)
- in patients with hyperlipidemia, evolocumab had a 52% likelihood of being cost-effective only when compared with statins alone using a threshold of $100,000 per QALY gained
- in high-risk patients with hyperlipidemia, evolocumab had a maximum likelihood of 86% versus statins alone and a maximum of 11% versus ezetimibe plus statins at a threshold of $100,000 per QALYs gained
- in SI patients with hyperlipidemia, evolocumab had a maximum likelihood of 93% versus no treatment, and a maximum of 38% versus ezetimibe alone using the $100,000 per QALY gained threshold.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Ezetimibe efficacy in lowering LDL cholesterol:** The manufacturer derived the clinical effect estimates for ezetimibe in patients with primary hyperlipidemia and/or mixed dyslipidemia, high-risk patients with hyperlipidemia, and HeFH patient populations from the GAUSS-2 trial: an ezetimibe-controlled study comparing two doses of evolocumab (140 mg or 420 mg) with matching placebo plus ezetimibe 10 mg daily, over a treatment period of 12 weeks in patients who tried at least two statins and were unable to tolerate any dose or an increase in statin dose above the total weekly maximum doses.[11] Therefore, the treatment effects of ezetimibe, as add-on to ongoing statin therapy, may have been underestimated in the analyses conducted by the manufacturer in the patient populations with primary hyperlipidemia, high-risk patients with hyperlipidemia, and HeFH, in which ezetimibe was modelled without the added efficacy of background statin therapy. The manufacturer could have derived the efficacy estimates for ezetimibe added on to statins from the LAPLACE-2 study (Robinson et al.[5]), which included an ezetimibe plus statins group. Reanalyses conducted by the CADTH Common Drug Review (CDR) used alternative efficacy estimates for ezetimibe when added to background statin therapy.

- **Uncertainty surrounding efficacy of evolocumab in reducing CV event risk:** The manufacturer modelled the impact of LDL cholesterol reduction by evolocumab on cardiovascular event risks according to the results of the meta-analysis by Baigent et al.[7] of more than 170,000 patients in 26 trials of statin.[1] The manufacturer's economic submission indicated that the results from Baigent et al.[7] for "more versus less statins" patient populations were incorporated in the model, as the manufacturer considered that such populations and treatments resembled the target populations for evolocumab in this analysis.[1] Upon verification of the included inputs, CDR noticed that the rate ratios from Baigent et al.[7] may not have consistently represented similar populations. While estimates for ACS and IS were from the "more versus less statin" studies, the estimates for CHD and fatal IS were derived from the overall populations included in the meta-analysis, despite a reported CHD death rate ratio in the "more versus less statin" group.
- **Model time horizon and treatment duration:** The manufacturer's base-case analysis assumed a lifetime time horizon up to the age of 120 years, and duration of treatment up to 75 years. The extended durations (for both time horizon and treatment) are likely too long, considering the lack of long-term data to support the assumption of continued efficacy and benefits associated with evolocumab administration, as well as the patients' starting age (59 years) in the model.[1] It is very unlikely that patients aged 59 years and older with hyperlipidemia, familial or non-familial, could experience life gains extending to the age of 120 years old, nor could they continue to receive treatments for an additional 75 years.
- **Source for health state utility values:** The health state utilities in the default model were based on values from an industry-funded trial by Matza et al.,[13] despite the availability of Canadian utility data for CV events. The manufacturer's rationale for this inclusion was based on the utility data requirements for the proposed model structure and proposed health states, and on the variability in instruments and questionnaires used to elicit preferences. Although CDR reanalysis using alternative utility values did not significantly alter the results, the uncertainty in the proposed health states and corresponding utilities warrants further research.
- **Annual costs of statin therapy:** The manufacturer's classification of statin intensity levels was based on published literature and not on the statin strengths used in the clinical trials for evolocumab in the relevant patient populations. In addition, the calculation of the annual costs of statins in the model did not correspond to calculations made based on publicly available reimbursement prices for statins in Canada.
- **Dosing regimen for evolocumab:** The submitted product monograph for evolocumab includes a 420 mg once-monthly dosing regimen using three injections of 140 mg; the manufacturer indicated that the 420 mg monthly dosing was not included in the submitted analysis, as it is to be administered in an automatic mini-doser that is not currently available.[17] However, based on the product monograph, and confirmed by the clinical expert, the 420 mg monthly dose can be administered using three injections of the 140 mg/mL pre-filled auto-injector, currently available. The 420 mg once-monthly dose might be preferred by some patients and physicians to improve patient compliance, and this view is supported by the results of the submitted clinical trials for evolocumab efficacy (LAPLACE-2, RUTHERFORD-2, and GAUSS-2)[5,6,11] that included the 420 mg once-monthly regimen and concluded that efficacy between the 140 mg dose every two weeks and the 420 mg once-monthly regimens was similar. Use of a 420 mg once-monthly regimen would increase the total costs associated with evolocumab therapy, as shown in a CDR reanalysis using annual costs of evolocumab based on 420 mg once-monthly dosing regimen (Table 25 in Appendix 4).

5. CADTH COMMON DRUG REVIEW REANALYSES

Efficacy of ezetimibe in lowering LDL cholesterol when used in combination with a statin
Reanalyses were conducted using the reductions in LDL cholesterol observed in the clinical trials submitted by the manufacturer (LAPLACE-2, RUTHERFORD-2, and PROFICIO).[5,6,18] Based on the CDR reanalyses, the ICUR for evolocumab plus background statins, compared with ezetimibe plus background statins, in patients with hyperlipidemia varied up to $225,083 per QALY; in high-risk patients with hyperlipidemia, the ICUR increased up to $166,583 per QALY. In patients with HeFH, the ICUR for evolocumab plus high-intensity statins, compared with ezetimibe plus high-intensity statins, increased up to $46,360 per QALY (Table 19 in Appendix 4).

Treatment effects of evolocumab in reducing cardiovascular event risk
CDR conducted a reanalysis using the rate ratio for CHD death from the "more versus less statins" group rather than the rate ratio from the overall population, as used by the manufacturer. This reanalysis improved representation of the included patient populations (more intense statin regimens) and enabled a reassessment of the manufacturer's results. In patients with primary hyperlipidemia, the ICUR for evolocumab ranged from $109,885 to $164,854 per QALY. In high-risk patients with hyperlipidemia, the ICUR for evolocumab ranged from $91,048 to $131,679 per QALY. In SI patients, the ICUR for evolocumab ranged from $62,811 to $114,019 per QALY. The ICUR for evolocumab did not vary significantly in patients with HeFH (Table 20 in Appendix 4).

Alternative source for health states utilities
CDR conducted reanalyses using alternative utility values based on publications by Sullivan et al.[19,20] Results of the CDR reanalyses were very similar to those reported by the manufacturer in the base-case analyses.

Impact of adjusting costs of statins
The annual costs in the economic model for included statins were adjusted to reflect the classification of intensity, as reported in the LAPLACE-2 trial (Robinson et al.[5]) and using publicly available unit prices (Ontario Drug Benefit).[15] Similar to the manufacturer's assumption, only the least expensive alternative within each statin intensity category was chosen in the CDR reanalysis, excluding pharmacy mark-up and dispensing fees. The results of adjusting the statin intensity and annual costs did not impact the manufacturer's base-case results (Table 22 in Appendix 4).

Model time horizon and duration of treatment
CDR conducted a sensitivity analysis using a more realistic and clinically applicable duration of 20 years as the time horizon and a treatment duration based on the time horizon used in the recently published technology assessment by the Institute for Clinical and Economic Review on the comparative effectiveness of PCSK9 inhibitors for treatment of high cholesterol levels (The New England Comparative Effectiveness Public Advisory Council, 2015).[21] The ICURs for evolocumab varied when the time horizon was reduced to 20 years: in patients with primary hyperlipidemia, $164,152 to $245,422 per QALY; in high-risk patients with hyperlipidemia, $109,245 to $160,022 per QALY; in HeFH patients, $22,524 to $46,448 per QALY; in SI patients, $87,934 to $158,772 per QALY (Table 23 in Appendix 4).

CADTH Common Drug Review multi-way sensitivity analysis
CDR conducted a multi-way sensitivity analysis that incorporated an efficacy estimate for ezetimibe of 31.05% in patients with hyperlipidemia and 24.91% in patients with HeFH (as observed in the submitted clinical trials of LAPLACE-2, RUTHERFORD-2, and PROFICIO),[5,6,18] a rate ratio for CHD death of 0.85, a

time horizon and treatment duration reduced to 20 years, and adjusted annual costs of background statin therapy. Summary results are presented in Table 3.

TABLE 3: SUMMARY RESULTS OF CADTH COMMON DRUG REVIEW MULTI-WAY SENSITIVITY ANALYSIS

		ICUR ($/QALY)			
	Comparators	Primary hyperlipidemia	High-risk hyperlipidemia	HeFH	SI
Base case[a]	Medium- or high-intensity statins[b]	$100,482	$79,598	$18,457	$57,943
	Ezetimibe + medium- or high-intensity statins[c]	$151,112	$115,284	$34,744	$105,351
CDR multi-way sensitivity analysis	Medium- or high-intensity statins[b]	$180,427	$124,922	$23,822	$95,842
	Ezetimibe + medium- or high-intensity statins[c]	$397,180	$263,929	$68,813	$172,177

CDR = CADTH Common Drug Review; HeFH = heterozygous familial hypercholesterolemia; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SI = statin-intolerant.
[a] Manufacturer's base-case analysis.[1]
[b] Only high-intensity statins are modelled in the HeFH patient population; in SI patients, the comparator was no treatment.
[c] Ezetimibe was added to high-intensity statins in the HeFH patient population; in SI patients, the comparator was ezetimibe alone.

Dosing regimen for evolocumab (monthly versus biweekly)

CDR conducted a reanalysis that modified the annual cost of evolocumab in the model to reflect 420 mg once-monthly dosing instead of the base case of 140 mg every two weeks. The annual drug costs for evolocumab increased from $[redacted] to $[redacted] when three 140 mg injections are used every month at a price per injection of $[redacted].[1] Using the once-monthly regimen, the manufacturer's base-case ICURs increased up to $219,924 per QALY in patients with primary hyperlipidemia, $166,145 per QALY in high-risk patients with hyperlipidemia, $55,281 per QALY in HeFH patients, and $156,081 per QALY in SI patients. Using CDR multi-way analysis, a monthly regimen of evolocumab would increase ICURs up to $566,984 per QALY in primary hyperlipidemia patients, $376,657 per QALY in high-risk patients, $106,915 per QALY in HeFH patients, and up to $252,437 in SI patients (Table 25 in Appendix 4).

Additional price-reduction scenario

A price-reduction analysis was conducted on both the manufacturer's base-case analyses and the CDR multi-way sensitivity analysis in patients with hyperlipidemia (primary and high-risk). The results showed that, using the manufacturer's base-case analyses, a price reduction ranging from approximately 50% to 60% would reduce the ICURs of evolocumab to $33,335 per QALY, based on comparator used and target patient population (Table 26).

- Using CDR's multi-way sensitivity analysis based on adjusted efficacy for ezetimibe, impact of LDL cholesterol lowering on CHD death, and shorter time horizon, a price reduction ranging from approximately 50% to 80% would reduce the ICURs of evolocumab to $43,936 per QALY (Table 27).

6. ISSUES FOR CONSIDERATION

- **Comparator of interest:** The manufacturer's economic evaluation compared evolocumab plus background statins with ezetimibe in combination with background statins. Based on expert opinion, it is expected that evolocumab may be added to a combination therapy consisting of ezetimibe plus statin therapy in patients who require additional lowering of LDL cholesterol. The product monograph for evolocumab refers to the addition of evolocumab to ezetimibe *or* statins in patients with homozygous familial hypercholesterolemia, yet it is not clear from the product monograph whether evolocumab could be added to a combination of ezetimibe *and* statins.[3]

- **Costs and disutilities associated with adverse events:** The manufacturer's economic model did not include costs or disutilities associated with adverse events (AEs) based on results from the GAUSS-2, RUTHERFORD-2, and LAPLACE-2 phase 3 clinical trials that indicated no differences in the adverse event profile of evolocumab versus its comparators. As detailed in the CDR clinical review for evolocumab, the included studies were not powered to assess harms such as AEs, serious AEs, or withdrawal due to adverse events. The exclusion of AEs associated with evolocumab does not represent actual use of evolocumab in clinical practice.

7. PATIENT INPUT

Input was received from two patient groups: the Heart and Stroke Foundation of Canada and the Familial Hypercholesterolemia Canada Patient Network. The patient groups noted that their respondents expected that evolocumab would work to lower cholesterol levels more effectively and without the side effects experienced with statins. The manufacturer's cost-utility analysis was based on the clinical efficacy of evolocumab on lowering LDL cholesterol. Finally, none of the patients in the surveys had discontinued evolocumab; this was reflected in the manufacturer's economic model that assumed a compliance rate of 100%.

8. CONCLUSIONS

There are a number of limitations with how the evidence for the comparative clinical effectiveness of evolocumab versus ezetimibe was modelled in the economic analysis. This resulted in uncertainty in the assessment of evolocumab's cost-effectiveness versus ezetimibe in patients with hyperlipidemia and HeFH. In the analyses submitted by the manufacturer, the ICURs for evolocumab were more than $57,000 per QALY across all populations and subgroups, except in patients with HeFH, in which ICURs ranged from $18,457 to $34,744 per QALY when evolocumab was compared with background statin therapy or ezetimibe plus background statin therapy.

CDR reanalyses to address the identified limitations of the manufacturer's economic analysis showed that results were sensitive to ezetimibe efficacy when added to background statin therapy, to the impact of LDL cholesterol lowering on CHD death event risk, and to model time horizon and treatment duration across all populations and subgroups except in patients with HeFH. The ICURs for evolocumab added on to statins, when compared with ezetimibe plus background statins, were more than $100,000 per QALY, and as high as $397,000 per QALY in some patient subgroups. In patients with HeFH, the ICUR for evolocumab from CDR reanalyses increased by up to $68,813 per QALY.

Based on the limitations identified and for most of the patient populations included in this submission, evolocumab would require a reduction in price of 50% to 80% to be considered a cost-effective option compared with statins alone or ezetimibe plus statins, based on conventionally accepted thresholds.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 4 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus 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 as such 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 ($)	Recommended Dosage	Annual Cost ($)
Evolocumab (Repatha)	**140 mg/mL**	**pre-filled auto-injector**	**[redacted][a] per auto-injector**	**140 mg SC injection every 2 weeks OR 420 mg once monthly**	**[redacted] to [redacted][b]**
HMG-CoA Reductase Inhibitors (Statins)					
Rosuvastatin calcium (generics)	5 mg 10 mg 20 mg 40 mg	tab	0.2311 0.2437 0.3046 0.3582	10 to 40 mg daily	88.95 to 130.74
Atorvastatin calcium (generics)	10 mg 20 mg 40 mg 80 mg	tab	0.3138 0.3922 0.4216 0.4216	10 to 80 mg at bedtime	114.54 to 153.88
Fluvastatin sodium (generics)	20 mg 40 mg	cap	0.2202 0.3092	20 to 40 mg at bedtime	80.37 to 112.86
Fluvastatin sodium (Lescol XL)	80 mg	tab	1.5514	80 mg daily	566.26
Lovastatin (generics)	20 mg 40 mg	tab	0.4919 0.8985	20 to 80 mg at bedtime	179.54 to 655.91
Pravastatin sodium (generics)	10 mg 20 mg 40 mg	tab	0.4050 0.4778 0.5755	10 to 40 mg at bedtime	147.83 to 210.06
Simvastatin (generics)	5 mg 10 mg 20 mg 40 mg 80 mg	tab	0.1841 0.3642 0.4501 0.4501 0.4501	10 to 80 mg at bedtime	132.93 to 164.29
Cholesterol Absorption Inhibitor					
Ezetimibe (Ezetrol)	10 mg	tab	0.4612	10 mg daily	168.34

cap = capsule; SC = subcutaneous; tab = tablet.
[a] Source: Manufacturer's submitted confidential price.[1]
[b] 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 online drug plan formulary October 2015 unless indicated otherwise.[15]

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 to 145 mg daily	129.94 to 332.62
Bezafibrate (Bezalip and generics)	400 mg	tab	2.2170	400 mg every morning or at bedtime	809.21
Micro-coated fenofibrate (Lipidil Supra and generics)	160 mg	tab	0.3116	160 mg daily	113.73
Fenofibrate (Lipidil and generics)	100 mg	cap	0.6105	3 to 4 caps divided three times daily before meals	668.50 to 891.33
Fenofibrate (Lipidil Micro and generics)	67 mg 200 mg	cap	0.4714[a] 0.2723	67 to 200 mg daily	99.39 to 172.06
Gemfibrozil (Lopid and generics)	300 mg	cap	0.1340	600 mg b.i.d. a.c.	48.91
Binders/bile acid sequestrants					
Colesevelam (Lodalis)	625 mg	tab	1.1154	2.5 to 4.5 g daily	1,628.48 to 2,849.85
Cholestyramine resin (Questran, Olestyr and generics)	4 g/packet	oral powder	1.3167	one packet 1 to 6 times daily	480.60 to 2,883.57
Colestipol 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	348.57 to 2,091.45

a.c. = before meals; b.i.d. = twice daily; cap = capsule; tab = tablet.

[a] Source: Newfoundland formulary October 2015.[22]

Note: Flush-free niacin, available over-the-counter, would not be a relevant comparator as it contains no free nicotinic acid. It is not effective in the treatment of dyslipidemia and is not included.

Source: Ontario online drug plan formulary October 2015 unless indicated otherwise.[15]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 6: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS EVOLOCUMAB PLUS MEDIUM- OR HIGH-INTENSITY STATINS RELATIVE TO MEDIUM- OR HIGH-INTENSITY STATINS ALONE IN PATIENTS WITH NON-FAMILIAL HYPERLIPIDEMIA AND/OR MIXED DYSLIPIDEMIA?

Evolocumab[a] vs. Medium or High-Intensity Statins	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	$100,482 per QALY $150,153 per life-year					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.
[a] Evolocumab plus medium- or high-intensity statins.
Note: Based on manufacturer's results.[1]

TABLE 7: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS EVOLOCUMAB PLUS MEDIUM- OR HIGH-INTENSITY STATINS RELATIVE TO EZETIMIBE PLUS MEDIUM- OR HIGH-INTENSITY STATINS IN PATIENTS WITH NON-FAMILIAL HYPERLIPIDEMIA AND/OR MIXED DYSLIPIDEMIA?

Evolocumab[a] vs. Ezetimibe[a]	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	$151,112 per QALY $223,822 per life-year					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.
[a] Treatment plus medium- or high-intensity statins.
Note: Based on manufacturer's results.[1]

TABLE 8: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS EVOLOCUMAB PLUS MEDIUM- OR HIGH-INTENSITY STATINS RELATIVE TO MEDIUM- OR HIGH-INTENSITY STATINS ALONE IN HIGH-RISK PATIENTS WITH NON-FAMILIAL HYPERLIPIDEMIA AND/OR MIXED DYSLIPIDEMIA?

Evolocumab[a] vs. Medium or High-Intensity Statins	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	$79,598 per QALY $85,008 per life-year					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.
[a] Evolocumab plus medium- or high-intensity statins.
Note: Based on manufacturer's results.[1]

TABLE 9: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS EVOLOCUMAB PLUS MEDIUM- OR HIGH-INTENSITY STATINS RELATIVE TO EZETIMIBE PLUS MEDIUM- OR HIGH-INTENSITY STATINS IN HIGH-RISK PATIENTS WITH NON-FAMILIAL HYPERLIPIDEMIA AND/OR MIXED DYSLIPIDEMIA?

Evolocumab[a] vs. Ezetimibe[a]	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	$115,284 per QALY $121,617 per life-year					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.
[a] Treatment plus medium- or high-intensity statins.
Note: Based on manufacturer's results.[1]

TABLE 10: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS EVOLOCUMAB PLUS HIGH-INTENSITY STATINS RELATIVE TO HIGH-INTENSITY STATINS ALONE IN PATIENTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA?

Evolocumab[a] vs. High-Intensity Statins	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	$18,457 per QALY $20,054 per life-year					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.
[a] Evolocumab plus high-intensity statins.
Note: Based on manufacturer's results.[1]

TABLE 11: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS EVOLOCUMAB PLUS HIGH-INTENSITY STATINS RELATIVE TO EZETIMIBE HIGH-INTENSITY STATINS IN PATIENTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA?

Evolocumab[a] vs. Ezetimibe[a]	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	$34,744 per QALY $37,863 per life-year					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.
[a] Treatment plus high-intensity statins.
Note: Based on manufacturer's results.[1]

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 12: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	None		
Was the material included (content) sufficient?	X		
Comments	None		
Was the submission well organized and was information easy to locate?		X	
Comments	None		

TABLE 13: AUTHOR 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	

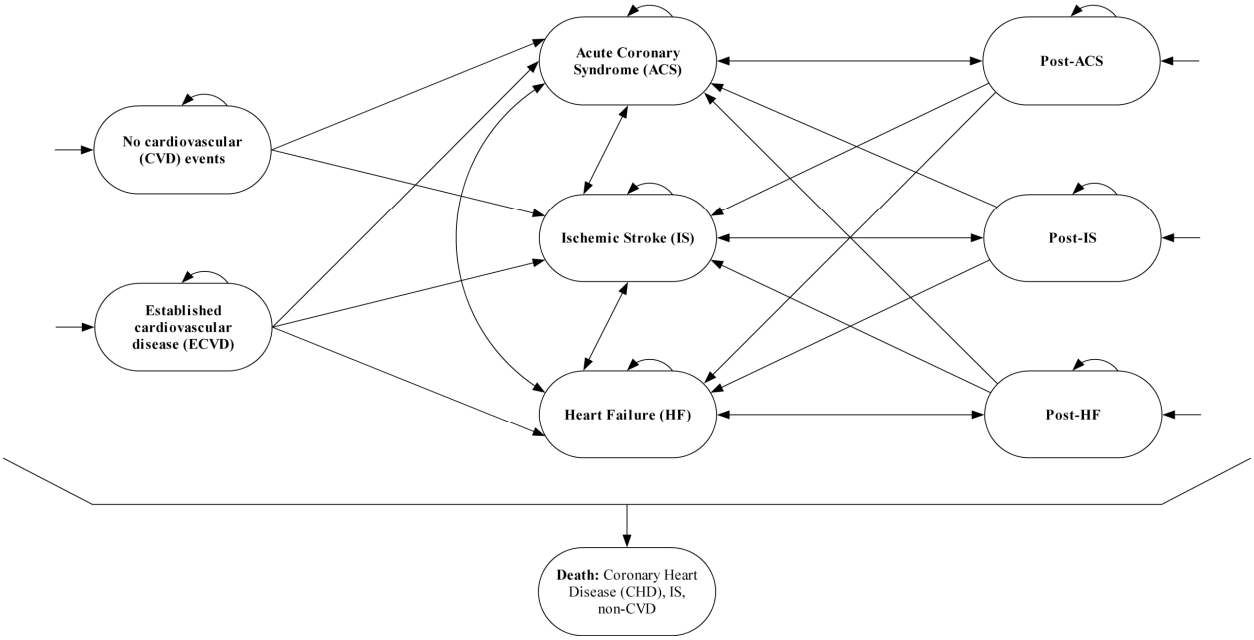
CDR = CADTH Common Drug Review.

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The developed model considers a cohort of patients within a state-transition model, where the cohort is followed until death. The model allows for transition through three categories of cardiovascular (CV) health states (entry, acute, and chronic), where at the end of every cycle, patients could either transition to another health state or remain in their current health state. The cycle length was set at one year. Entry into the model can be via one of two entry health states or via a post–CV-disease (CVD) health state, depending on the patient's CV history. The two entry health states are "No CVD" and "Established CVD" (ECVD); patients could remain in these entry states for several cycles. However, once they progressed, they could not return to these states. The rationale being that, once a patient has experienced a CV event (e.g., ischemic stroke [IS]) and has moved to the post-CVD state (e.g., post-IS), this patient could not return to a less severe health state (No CVD or ECVD) as if the more severe CV event had never occurred. Patients with a history of CV events (i.e., acute coronary syndrome [ACS], IS, and heart failure [HF]) start in the corresponding post-CVD health state. Acute health states are ACS, IS and HF, meaning that patients would move to the post-acute health states after one cycle unless they experienced another event, which could be the same acute CV event again or a different one. Patients can remain in chronic (or post-CVD) health states for several cycles, with the fatal health states being the final states, i.e., absorbing states. The model also contains multiple combined post-CVD health states to keep track of patients' disease history, which may contain up to three CV events. The manufacturer indicated that the advantage of these additional combined health states was that they allowed the cohort to experience recurring CV events in the long term, without losing track of the crucial part of the event history of patients.[1] The manufacturer's base-case analysis assumed a lifetime time horizon up to the maximum patient age of 120 years old and an assumed duration of treatment of up to 75 years after entering the model.[1] LDL cholesterol lowering observed in phase 3 trials (LAPLACE-2 , RUTHERFORD-2, and GAUSS-2)[5,6,11] was assumed to be maintained for duration of treatment, which was assumed to be lifetime in the base-case scenario.[1] As baseline risk was predicted using risk functions, a maximum age of 75 years old was introduced, with no further increase in risk past that age.[1]

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE



Source: Manufacturer's pharmacoeconomic submission.[1]

TABLE 14: DATA SOURCES

Data Input	Description of Data Source	Comment

Efficacy	• Estimates of LDL-C reduction from baseline were obtained from multiple phase 3 trials:
	  ○ LAPLACE-2 (Robinson et al.[5]): for efficacy of evolocumab in all patients with non-familial primary hyperlipidemia and/or mixed dyslipidemia and high-risk patients with non-familial hyperlipidemia and/or mixed dyslipidemia with a prior CV event
	  ○ RUTHERFORD-2 (Raal et al.[6]) for evolocumab in patients with HeFH
	• Impact of LDL-C reduction on CV events was based on results of a published meta-analysis by Baigent et al. of more than 170,000 patients enrolled in 26 trials of statins.[7]
		GAUSS-2 was ezetimibe-controlled, comparing the two approved doses of evolocumab (140 mg or 420 mg) with ezetimibe 10 mg daily, without background statin therapy;[11] however, ezetimibe was modelled as add-on to statin in hyperlipidemia and HeFH patients.

Natural history	• For patients with primary hyperlipidemia and/or mixed dyslipidemia, baseline CV risk was based on Framingham risk predictions for a primary CV event (D'Agostino et al.).[8] • For high-risk patients with primary hyperlipidemia and/or mixed dyslipidemia with prior CV events, baseline CV risk was based on the Reduction of Atherothrombosis for Continued Health (REACH) risk prediction engine for recurrent events (Wilson et al.).[9] • In HeFH patients, the baseline CV event risk was based on the study by Benn et al. describing the CV event risk for HeFH versus high-risk non-HeFH patients.[10]	Appropriate

Data Input	Description of Data Source	Comment
Utilities	• Baseline utility was based on a Canadian publication by Feeny et al.[12] • CV health state utilities were sourced from a UK utility study of 200 individuals that rated health states in time trade-off (TTO) interviews (Matza et al.).[13]	Study by Matza et al.[13] was industry-funded.
Resource use		
Adverse events (indicate which specific adverse events were considered in the model)	The model did not include incidence, cost, or health-related quality of life effects of adverse events based on findings from phase 3 trials that reported evolocumab to be well-tolerated or with no notable difference in adverse events compared with placebo and ezetimibe.[5,6,11,23]	
Mortality	• Mortality from non-CV causes was taken from Canadian national life tables (Statistics Canada 2013) by age and gender.[24] • Proportion of overall deaths that were CV-specific were obtained from Statistics Canada (2014).[25]	Appropriate
Costs		
Drug	Unit costs for drugs were obtained from the Ontario Public Drug Program when available.[15]	• The least expensive alternative within each statin category was selected. • Manufacturer's estimation of costs for high-intensity and medium-intensity statins was inaccurate.
AEs	Cost and impact on quality of life for AEs were not included in the manufacturer's analysis.	
Health state	• The acute and long-term cost of UA, MI and HF were taken from a publication by Goeree et al.[14] • The first year cost of IS was taken a publication by Mittmann et al.[26] • The costs of fatal UA, MI, IS, and HF were taken from a 2010 Canadian publication reporting of the REACH study (Smolderen et al.).[27]	

AE = adverse event; CV = cardiovascular; HeFH = heterozygous familial hypercholesterolemia; HF = heart failure; IS = ischemic stroke; LDL-C = low-density–lipoprotein cholesterol; MI = myocardial infarction; REACH = Reduction of Atherothrombosis for Continued Health; TTO = time trade-off; UA = unstable angina.

TABLE 15: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Risk factors for risk prediction taken from phase 3 trial data regarding mean, standard deviations, and proportions unless locally relevant target population patient characteristics available.	Appropriate Confirmed by clinical expert as being representative of clinical practice.
Based on a corrected RR for HeFH patients versus high-risk non-HeFH patients; the corrected RR is applied on the baseline CV event risk for high-risk non-HeFH patients.	Appropriate.
When baseline risk is predicted using risk functions, a maximum age is introduced, over and above which there is no further increase in risk; this age is currently set at 75 years in the base case.	Discussed in point (1) following table.
LDL-C lowering observed in 12 weeks; phase 3 trials assumed to be maintained for duration of treatment, which is assumed to be lifetime in base case.	Uncertain. No long-term evidence available indicating patients will not be tolerant to evolocumab over model lifetime.
The observed relationship between LDL-C lowering and CV event risk reduction in the CTTC analyses is assumed to be applicable to LDL-C reduction for both statin and non-statin-based lipid-lowering therapy (including PCSK9 inhibitors).	Discussed in point (2) following table.
LDL-C lowering effect on HF incidence was not reported in CTTC 2010 meta-analyses; assumed to be equal to reported RR per mmol/L LDL-C reduction as for MI.	Likely appropriate, although more data on long-term impact of LDL-C reduction on CV events is required.
An LDL-C effect threshold of 40 mg/dL is assumed, below which further LDL-C reductions will not translate into added benefits in reduced CV risk.	Appropriate.
Lifetime horizon includes modelling up to a maximum age of 120 years old.	Discussed in point (3) following table.
Only one event can occur at each cycle in the model.	Discussed in point (4) following table.
Separate health states are included for acute and long-term events capturing the different levels of costs and utility in the acute and long-term periods, respectively. Once an event occurs, the patient spends the cycle in the acute health state. Following this, the patient moves to the post-acute event health state until a new event (or death) occurs.	Appropriate.
Combined health states are introduced to regain some memory in the cohort model, allowing the lowest utility, highest cost and highest transition probability of combined events health states.	Appropriate.
Health state utility values estimated using TTO method; constant background utility applied across age groups.	Likely appropriate.
Treatment is assumed lifelong in base case.	Refer to point (3) following table.
Full compliance to therapy is assumed in base case.	Uncertain. There is no long-term evidence to support full compliance.

CTTC = Cholesterol Treatment Trialists' Collaboration; CV = cardiovascular; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density–lipoprotein cholesterol; MI = myocardial infarction; PCSK9 = Proprotein Convertase Subtilisin/Kexin type 9; RR = relative risk; TTO = time trade-off.

1. This assumption is likely appropriate, despite lack of evidence determining the maximum age beyond which no further increase in risk is observed. The submitted model does not permit the modification of this variable to allow a higher age limit, although its impact on the results is expected to be insignificant.
2. Likely appropriate. Expert opinion supports that LDL cholesterol reduction is key to reducing CV events, regardless of the type of intervention or therapeutic category involved.
3. Inappropriate and possibly excessive, considering the starting patient age in the economic model was approximately 60 years. However, despite support from clinical expert opinion concerning the expected long-term use of evolocumab, there is a lack of available long-term evidence concerning the efficacy of evolocumab in lowering LDL cholesterol levels and CV events.
4. It may be an oversimplification to assume that patients will experience only one event per year. However, this assumption may be an inevitable property of the Markov cohort state-transition model that was used for this analysis.

Manufacturer's Results

Full Health Canada Indication

The first analysis evaluated the cost utility of evolocumab plus medium- or high-intensity statins in patients with non-familial hyperlipidemia and/or mixed dyslipidemia. The manufacturer indicated that treatment with evolocumab added to medium- or high-intensity statins was associated with incremental costs, quality-adjusted life-years (QALYs), and life-years when compared with medium- or high-intensity statins alone or in combination with ezetimibe. The resulting incremental cost-utility ratios (ICURs) were $100,482 and $151,112 per QALY when compared with medium- or high-intensity statins alone and with ezetimibe plus medium- or high-intensity statins, respectively (Table 16).

TABLE 16: INCREMENTAL COST-EFFECTIVENESS OF EVOLOCUMAB PLUS MEDIUM- OR HIGH-INTENSITY STATINS VERSUS MEDIUM- OR HIGH-INTENSITY STATINS AND EZETIMIBE PLUS MEDIUM- OR HIGH-INTENSITY STATINS IN PATIENTS WITH HYPERLIPIDEMIA

	Evolocumab + Medium- or High-Intensity Statins	Comparator	
		Medium- or High-Intensity Statins	Ezetimibe + Medium- or High-Intensity Statins
Rates			
CVD events	0.54	0.97	0.83
Non-fatal CVD events	0.36	0.72	0.60
UA/MI	0.11	0.26	0.21
IS	0.14	0.36	0.29
HF	0.10	0.10	0.10
Fatal CVD events	0.18	0.25	0.23
CHD death	0.09	0.17	0.14
Stroke death	0.08	0.09	0.09
Non-CVD mortality	0.82	0.75	0.77
Costs			
Medication	$61,092	$1,121	$3,336
CVD events	$7,113	$14,276	$11,815
Non-fatal acute CVD events	$5,048	$11,522	$9,275
UA/MI	$572	$1,312	$1,064
IS	$3,694	$9,417	$7,423
HF	$783	$794	$789
Fatal CVD events	$2,065	$2,754	$2,540
CHD death	$883	$1,544	$1,339
IS death	$1,182	$1,210	$1,201
Non-acute CVD events	$22,621	$26,162	$25,054
Total cost	**$90,826**	**$41,559**	**$40,205**
Incremental cost	**–**	**$49,266**	**$50,621**
Total QALY	**10.91**	**10.42**	**10.58**
Incremental QALYs	**–**	**0.49**	**0.33**
ICUR ($/QALY gained)	**–**	**$100,482**	**$151,112**
Total LY	**13.32**	**12.99**	**13.09**
Incremental LY	**–**	**0.33**	**0.23**
ICER ($/LY gained)	**–**	**$150,153**	**$223,822**

CHD = coronary heart disease; CVD = cardiovascular disease; HF = heart failure; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; IS = ischemic stroke; MI = myocardial infarction; IS = ischemic stroke; LY = life-year; QALY = quality-adjusted life-year; UA = unstable angina.
Source: Adapted from manufacturer's pharmacoeconomic submission, Table 12 (page 35).[1]

High-Risk Patients With Primary Hyperlipidemia or Mixed Dyslipidemia Who Have Experienced a prior Cardiovascular Event and Who Cannot Reach the LDL Cholesterol Target With Standard of Care

In high-risk patients with primary hyperlipidemia and/or mixed dyslipidemia with a prior CV event, similar results were reported: treatment with evolocumab plus medium- or high-intensity statins was associated with incremental costs, QALYs, and LYs when compared with medium- or high-intensity statins alone and ezetimibe plus medium- or high-intensity statins. The resulting ICURs were $79,598 and $115,284 per QALY when compared with medium- or high-intensity statins alone and with ezetimibe plus medium- or high-intensity statins, respectively (Table 17).

TABLE 17: INCREMENTAL COST-EFFECTIVENESS OF EVOLOCUMAB PLUS MEDIUM- OR HIGH-INTENSITY STATINS VERSUS MEDIUM- OR HIGH-INTENSITY STATINS ALONE AND VERSUS EZETIMIBE PLUS MEDIUM- OR HIGH-INTENSITY STATINS IN HIGH-RISK PATIENTS WITH PRIMARY HYPERLIPIDEMIA AND/OR MIXED DYSLIPIDEMIA WITH A PRIOR CARDIOVASCULAR EVENT

	Evolocumab + Medium or High-Intensity Statins	Comparator	
		Medium or High-Intensity Statins	Ezetimibe + Medium or High-Intensity Statins
Rates			
CVD Events	0.84	1.31	1.16
Non-fatal CVD events	0.57	0.95	0.82
UA/MI	0.15	0.33	0.27
IS	0.15	0.38	0.30
HF	0.27	0.24	0.25
Fatal CVD events	0.27	0.37	0.34
CHD death	0.18	0.28	0.25
Stroke death	0.09	0.09	0.09
Non-CVD mortality	0.73	0.63	0.66
Costs			
Medication	$55,266	$933	$2,971
CVD events	$10,822	$19,730	$16,756
Non-fatal acute CVD	$7,543	$15,335	$12,683
events	$822	$1,888	$1,540
UA/MI	$4,401	$11,296	$8,944
IS	$2,320	$2,150	$2,198
HF	$3,279	$4,395	$4,073
Fatal CVD events	$1,797	$2,950	$2,619
CHD death	$1,482	$1,445	$1,455
IS death	$57,215	$55,930	$56,309
Non-acute CVD events			
Total cost	**$123,303**	**$76,653**	**$76,036**
Incremental cost	**–**	**$46,650**	**$47,267**
Total QALY	**8.92**	**8.34**	**8.51**
Incremental QALY	**–**	**0.59**	**0.41**
ICUR ($/QALY gained)	**–**	**$79,598**	**$115,284**
Total LY	**12.05**	**11.50**	**11.66**
Incremental LY	**–**	**0.55**	**0.39**
ICER ($/LY gained)	**–**	**$85,008**	**$121,617**

CHD = coronary heart disease; CVD = cardiovascular disease; HF = heart failure; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; IS = ischemic stroke; MI = myocardial infarction; IS = ischemic stroke; LY = life-year; QALY = quality-adjusted life-year; UA = unstable angina.
Source: Adapted from manufacturer's pharmacoeconomic submission, Table 13 (page 39).[1]

Heterozygous Familial Hypercholesterolemia

In patients with heterozygous familial hypercholesterolemia (HeFH), the manufacturer reported that treatment with evolocumab with high-intensity statins was associated with incremental costs, QALYs, and LYs when compared with high-intensity statins alone and ezetimibe plus high-intensity statins. The resulting ICURs were $18,457 and $34,744 per QALY when compared with high-intensity statins alone and with ezetimibe plus high-intensity statins, respectively (Table 18).

TABLE 18: INCREMENTAL COST-EFFECTIVENESS OF EVOLOCUMAB PLUS HIGH-INTENSITY STATINS COMPARED WITH HIGH-INTENSITY STATINS AND EZETIMIBE PLUS HIGH-INTENSITY STATINS IN PATIENTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

	Evolocumab + High-Intensity Statins	Comparator	
		High-Intensity Statins	Ezetimibe + High-Intensity Statins
Rates			
CVD Events	2.39	3.55	3.14
Non-fatal CVD events	1.63	2.70	2.32
UA/MI	0.54	1.08	0.89
IS	0.57	1.20	0.98
HF	0.52	0.41	0.44
Fatal CVD events	0.75	0.85	0.83
CHD death	0.44	0.60	0.55
Stroke death	0.32	0.26	0.28
Non-CVD mortality	0.25	0.15	0.17
Costs			
Medication	$53,317	$915	$2,760
CVD events	$30,805	$56,609	$47,004
Non-fatal acute CVD events	$22,124	$46,124	$37,086
UA/MI	$3,038	$6,588	$5,281
IS	$15,253	$36,207	$28,312
HF	$3,834	$3,329	$3,494
Fatal CVD events	$8,681	$10,485	$9,918
CHD death	$4,107	$6,293	$5,594
IS death	$4,574	$4,192	$4,324
Non-acute CVD events	$25,561	$25,392	$25,905
Total cost	**$109,683**	**$82,916**	**$75,669**
Incremental cost	**–**	**$26,767**	**$34,014**
Total QALY	**9.16**	**7.71**	**8.18**
Incremental QALY	**–**	**1.45**	**0.98**
ICUR ($/QALY gained)	**–**	**$18,457**	**$34,744**
Total LY	**11.62**	**10.28**	**10.72**
Incremental LY	**–**	**1.33**	**0.90**
ICER ($/LY gained)	**–**	**$20,054**	**$37,863**

CHD = coronary heart disease; CVD = cardiovascular disease; HF = heart failure; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; IS = ischemic stroke; MI = myocardial infarction; IS = ischemic stroke; LY = life-year; QALY = quality-adjusted life-year; UA = unstable angina.
Source: Adapted from manufacturer's pharmacoeconomic submission, Table 14 (page 43).[1]

Manufacturer's Sensitivity Analyses

In addition to the base-case analyses, the manufacturer conducted probabilistic analyses and univariate sensitivity analyses to assess the uncertainty associated with the model parameters. Uncertainty in input parameters was also explored through univariate one-way sensitivity analyses, which were conducted using the 95% lower and upper bounds for clinical and utility data while unit costs were varied by +/-20%. The impact of uncertainty due to other model assumptions (e.g., treatment duration, compliance, discount rates) was also assessed. The results of the manufacturer's sensitivity analyses indicate that the model results are sensitive to the effect of LDL cholesterol lowering on risk of IS in every submitted patient population. In the primary hyperlipidemia analysis, the results are also sensitive to changes in baseline utility, treatment duration, and the effect of LDL cholesterol lowering on risk of IS

and death due to coronary heart disease (CHD). In the high-risk patients with hyperlipidemia, the results were also sensitive to treatment duration and effect of LDL cholesterol lowering on IS and CHD death.

Probabilistic Sensitivity Analysis

The manufacturer performed the PSA by conducting 1,000 Monte Carlo simulations in which values of key parameters were drawn randomly and independently from the parameter distributions. Standard errors were used for the parameter distribution.[16] Beta distributions were used for utilities and estimates for treatment effects on LDL cholesterol, gamma distributions were used for costs, and lognormal distributions were used for the other parameters.[16] The CEACs indicated the following:

1. In the primary hyperlipidemia population: Evolocumab plus medium- or high- intensity statins versus medium- or high- intensity statins alone had likelihoods of being cost-effective of 0% and 52% using thresholds of $50,000 and $100,000 per QALY gained, respectively. When compared with ezetimibe plus medium- or high- intensity statins, evolocumab had a 0% likelihood of being cost-effective, regardless of the threshold used.
2. In the high-risk patients with hyperlipidemia: Evolocumab plus medium- or high- intensity statins versus medium- or high-intensity statins alone had likelihoods of being cost-effective of 0% and 86% using thresholds of $50,000 and $100,000 per QALY gained, respectively. When compared with ezetimibe plus medium- or high- intensity statins, evolocumab had likelihoods of 0% and 11% using thresholds of $50,000 and $100,000 per QALY gained, respectively.
3. In patients with HeFH: Evolocumab plus high-intensity statins versus high-intensity statins alone had likelihoods of being cost-effective of 96% and 99% using thresholds of $50,000 and $100,000 per QALY gained, respectively. When compared with ezetimibe plus high-intensity statins, evolocumab had likelihoods of 86% and 99% using thresholds of $50,000 and $100,000 per QALY gained, respectively.

CADTH Common Drug Review Reanalyses

Ezetimibe Efficacy in Lowering LDL Cholesterol

The manufacturer derived the effect estimates for ezetimibe in the primary hyperlipidemia and/or mixed dyslipidemia and HeFH patient populations from the GAUSS-2 trial, an ezetimibe-controlled study comparing two doses of evolocumab (140 mg or 420 mg) with matching placebo plus ezetimibe 10 mg daily, over a treatment period of 12 weeks in patients who tried at least two statins and have been unable to tolerate any dose or an increase in statin dose above the total weekly maximum doses.[11] Therefore, the treatment effects of ezetimibe, as add-on to ongoing statin therapy, may have been underestimated in the analyses conducted by the manufacturer in the patient populations with hyperlipidemia and HeFH.

CADTH Common Drug Review (CDR) conducted reanalyses using efficacies for ezetimibe plus ongoing statins in patients with primary hyperlipidemia and HeFH, derived from the LAPLACE-2,[5] RUTHERFORD-2,[6] and PROFICIO[18] studies, to explore the sensitivity of the manufacturer's base-case results to any variation in ezetimibe efficacy in lowering LDL cholesterol (Table 19). No reanalyses were conducted in the statin-intolerant (SI) patient group.

TABLE 19: SUMMARY RESULTS FOR CADTH COMMON DRUG REVIEW REANALYSIS OF EZETIMIBE EFFICACY

		ICUR ($/QALY)		
Source	**LDL-C Lowering**	**Primary Hyperlipidemia**	**High-Risk Hyperlipidemia**	**HeFH**
GAUSS-2[a] (Stroes et al. 2014)[11] (**manufacturer's base case**)	17.81%	$151,112	$115,284	$34,744
Using LAPLACE-2 (Robinson et al. 2014),[5] RUTHERFORD-2 (Raal et al. 2015),[6] and PROFICIO (Stroes et al. 2015)[18]	31.05%[b] 24.91%[c]	$225,083	$166,583	$46,360

HeFH = heterozygous familial hypercholesterolemia; ICUR = incremental cost-utility ratio; LDL-C = low-density–lipoprotein cholesterol; QALY = quality-adjusted life-year.

[a] Manufacturer's base-case analysis.[1]

[b] % LDL-C reduction versus placebo (statins) for ezetimibe was approximated by subtracting the pooled estimate for evolocumab versus ezetimibe from the estimate for evolocumab versus placebo; i.e., 72.25% – (44.9 + 37.5/2) = 77.25 – 41.2 = 31.05%.

[c] % LDL-C lowering efficacy for ezetimibe in HeFH patients was derived using the same principle applied to hyperlipidemia patients in RUTHERFORD-2 (Raal et al.)[6] and PROFICIO (Stroes et al.)[18] studies: 61.31% – 36.4% = 24.91%.

Treatment Effects of Evolocumab in Reducing Cardiovascular Event Risk

The manufacturer modelled the impact of LDL cholesterol reduction by evolocumab on cardiovascular event risks according to the results of the meta-analysis by Baigent et al.[7] of more than 170,000 patients in 26 trials of statins.[1] The manufacturer's economic submission indicated that the results from Baigent et al. for "more versus less statins" were incorporated in the model, as the manufacturer considered such populations and treatments to resemble the target populations for evolocumab in this analysis.[1] Upon verification of the included inputs, the rate ratios from Baigent et al.[7] may not have consistently represented similar populations. While estimates for acute coronary syndrome (ACS) and IS were from the "more versus less statin" studies, the estimates for CHD and fatal IS were derived from the overall populations included in the meta-analysis, despite a reported CHD death rate ratio in the "more versus less statin" group. The selection of a rate ratio of 0.8 for CHD death from the overall population (rather than the 0.85 ratio from the "more versus less statins" group) biases the results in favour of evolocumab. CDR conducted a reanalysis using the rate ratio for CHD death from the "more versus less statins" group to explore the sensitivity of the results to this variation (Table 20).

TABLE 20: SUMMARY RESULTS FOR CADTH COMMON DRUG REVIEW REANALYSIS OF DEATH DUE TO CORONARY HEART DISEASE

		ICUR ($/QALY)			
	Comparators	Primary Hyperlipidemia	High-Risk Hyperlipidemia	HeFH	SI
CHD death rate ratio from overall population (0.80)[a,b]	Medium- or high-intensity statins[c]	$100,482	$79,598	$18,457	$57,943
	Ezetimibe + medium- or high-intensity statins[d]	$151,112	$115,284	$34,744	$105,351
CDR reanalysis: CHD death rate ratio from "more versus less statins" populations (0.85)[b]	Medium or high-intensity statins[c]	$109,885	$91,048	$18,741	$62,811
	Ezetimibe + medium- or high-intensity statins[d]	$164,854	$131,679	$36,844	$114,019

CDR = CADTH Common Drug Review; CHD = coronary heart disease; HeFH = heterozygous familial hypercholesterolemia; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SI = statin-intolerant.
[a] Manufacturer's base-case analysis.[1]
[b] Rate ratios from Baigent et al.[7]
[c] Only high-intensity statins are modelled in the HeFH patient population; in SI patients the comparator was no treatment.
[d] Ezetimibe was added to high-intensity statins in the HeFH patient population; in SI patients the comparator was ezetimibe alone.

Alternative Source for Health States Utilities

The health state utilities in the default model were based on values from the industry-funded trial by Matza et al.[13] The manufacturer conducted univariate one-way sensitivity analyses to explore the uncertainty in utility data using the 95% lower and upper bounds. The manufacturer's results were robust to changes in health state utilities except for baseline utility in the hyperlipidemia patient population (both primary and high-risk). To further explore the sensitivity of the model results to variation in utilities, CDR conducted reanalyses using alternative utility values based on publications by Sullivan et al.[19,20] Results of the CDR reanalyses were very similar to those reported by the manufacturer in the base-case analyses.

Impact of Adjusting Costs of Statins

The manufacturer's economic submission included annual costs of ongoing statin therapy, either alone or in combination with ezetimibe in the primary hyperlipidemia and/or mixed dyslipidemia, high-risk hyperlipidemia, and HeFH patient populations. The classification of statins by intensity level followed a health technology assessment conducted in the United Kingdom (Law et al.; National Institute for Health and Care Excellence 2014).[1,28,29] The assumed strength of included statins did not correspond to the reported statin strengths in the LAPLACE-2 trial (Robinson et al.);[5] the calculated annual costs also did not correspond to reimbursement unit prices for the statins assumed by the manufacturer (Table 20). Therefore, annual costs in the economic model for included statins were adjusted to reflect the classification of intensity as reported in the LAPLACE-2 trial (Robinson et al.)[5] and using publicly available unit prices (Ontario Drug Benefit)[15] (Table 21). CDR conducted a reanalysis that included the adjusted annual costs of ongoing statin therapy in the submitted patient populations (Table 22). Similar to the manufacturer's assumption, only the least expensive alternative within each statin intensity category was chosen in the CDR reanalysis, excluding pharmacy mark-up and dispensing fees.

TABLE 21: COMPARISON OF INCLUDED STATIN COSTS

		Reported Statin	Unit Price[a]	Annual Cost
Manufacturer's economic submission	High-intensity statins	Atorvastatin 20 mg	$0.3922	$89.01[b]
	Medium-intensity statins	Rosuvastatin 10 mg	$0.2437	$84.41[b]
LAPLACE-2 trial[5]	High-intensity statins	Atorvastatin 80 mg	$0.4216	$153.99[c]
		Rosuvastatin 40 mg	$0.3582	$130.83[c]
	Medium-intensity statins	Atorvastatin 10 mg	$0.3138	$114.62[c]
		Rosuvastatin 5 mg	$0.2311	$84.41[c]

[a] Source: Ontario online drug plan formulary September 2015.[15]
[b] Source: Manufacturer's pharmacoeconomic submission.[1]
[c] Annual cost calculated by multiplying unit price by 365.25 days.

The results of adjusting the statin intensity and annual costs did not significantly impact the manufacturer's base-case results (Table 22).

TABLE 22: SUMMARY RESULTS OF CADTH COMMON DRUG REVIEW REANALYSIS USING ADJUSTED ANNUAL COSTS FOR STATIN THERAPY

		ICUR ($/QALY)			
	Comparators	Primary Hyperlipidemia	High-Risk Hyperlipidemia	HeFH	SI
Base case[a]	Medium- or high-intensity statins[b]	$100,482	$79,598	$18,457	$57,943
	Ezetimibe + medium- or high-intensity statins[c]	$151,112	$115,284	$34,744	$105,351
CDR reanalysis using adjusted annual costs for ongoing statin therapy	Medium- or high-intensity statins[b]	$100,494	$79,614	$18,495	No change
	Ezetimibe + medium- or high-intensity statins[c]	$151,123	$115,301	$34,782	No change

CDR = CADTH Common Drug Review; HeFH = heterozygous familial hypercholesterolemia; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SI = statin-intolerant.
[a] Manufacturer's base-case analysis.[1]
[b] Only high-intensity statins are modelled in the HeFH patient population; in SI patients, the comparator was no treatment.
[c] Ezetimibe was added to high-intensity statins in the HeFH patient population; in SI patients, the comparator was ezetimibe alone.

Model Time Horizon and Duration of Treatment

The manufacturer's base-case analysis assumed a lifetime time horizon up to the age of 120 years and duration of treatment up to 75 years. The extended durations (for both time horizon and treatment) are likely excessive, considering the patients' starting age in the model of 59 years old.[1] There is a lack of long-term evidence on the use of evolocumab beyond clinical trial duration. In addition, although a lifetime time horizon is expected to capture all incurred costs and benefits until patients enter the absorbing health state (i.e., death), it is very unlikely that patients aged 59 years and above with hyperlipidemia, familial or non-familial, could experience life gains extending to the age of 120 years old, nor could they continue to receive treatments for an additional 75 years. To that end, CDR conducted a

sensitivity analysis using a more realistic and clinically applicable duration of 20 years as the time horizon and treatment duration based the time horizon used in the recently published technology assessment by the Institute for Clinical and Economic Review on the comparative effectiveness of PCSK9 inhibitors for treatment of high cholesterol levels (The New England Comparative Effectiveness Public Advisory Council 2015).[21] The results are summarized in Table 23.

TABLE 23: SUMMARY RESULTS OF CADTH COMMON DRUG REVIEW REANALYSIS USING SHORTER TIME HORIZON AND TREATMENT DURATION

		ICUR ($/QALY)			
	Comparators	Primary Hyperlipidemia	High-Risk Hyperlipidemia	HeFH	SI
Base case[a]	Medium- or high-intensity statins[b]	$100,482	$79,598	$18,457	$57,943
	Ezetimibe + medium- or high-intensity statins[c]	$151,112	$115,284	$34,744	$105,351
CDR reanalysis using a time horizon and treatment duration of 20 years	Medium- or high-intensity statins[b]	$164,152	$109,245	$22,524	$87,934
	Ezetimibe + medium- or high-intensity statins[c]	$245,422	$160,022	$46,448	$158,772

CDR = CADTH Common Drug Review; HeFH = heterozygous familial hypercholesterolemia; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SI = statin-intolerant.
[a] Manufacturer's base-case analysis.[1]
[b] Only high-intensity statins are modelled in the HeFH patient population; in SI patients, the comparator was no treatment.
[c] Ezetimibe was added to high-intensity statins in the HeFH patient population; in SI patients, the comparator was ezetimibe alone.

CADTH Common Drug Review Multi-way Sensitivity Analysis

CDR conducted a multi-way sensitivity analysis that incorporated the following:

1. Efficacy estimate for ezetimibe was modified to 31.05% (up from 17.8%) in patients with hyperlipidemia (primary and with prior CV event) and to 24.91% (up from 17.8%) in HeFH patients, based on the efficacy estimates for ezetimibe added to medium- and high- intensity statins derived from the LAPLACE-2,[5] RUTHERFORD-2,[6] and PROFICIO[18] studies, to reflect expected LDL cholesterol lowering efficacy of ezetimibe when added to statin therapy. CDR considered this estimate to be a conservative assumption based on the availability of evidence on ezetimibe efficacy.
2. Rate ratio for CHD death was changed from 0.80 to 0.85 based on Baigent et al.[7] to be more representative of patients on statin regimens of increased intensity as compared with the overall population.
3. Model time horizon and treatment duration were reduced to a more realistic value of 20 years.
4. Annual costs of background statin therapy were adjusted.

The results of the CDR multi-way sensitivity analysis are presented in Table 24.

TABLE 24: RESULTS OF CADTH COMMON DRUG REVIEW MULTI-WAY SENSITIVITY ANALYSIS

	Comparator	CDR Incremental Cost ($)	CDR Incremental QALY	CDR ICUR ($/QALY)	Manufacturer Base-Case ICUR ($/QALY)[a]
Primary hyperlipidemia	Medium- or high-intensity statins	$43,294	0.24	$180,427	$100,482
	Ezetimibe + medium- or high-intensity statins	$45,324	0.11	$397,180	$151,112
High-Risk hyperlipidemia	Medium- or high-intensity statins	$40,789	0.33	$124,922	$79,598
	Ezetimibe + medium- or high-intensity statins	$42,728	0.16	$263,929	$115,284
HeFH	High-intensity statins	$20,854	0.88	$23,822	$18,457
	Ezetimibe + high-intensity statins	$31,855	0.46	$68,813	$34,744
SI	No treatment	$37,176	0.39	$95,842	$57,943
	Ezetimibe	$40,335	0.23	$172,177	$105,351

CDR = CADTH Common Drug Review; HeFH = heterozygous familial hypercholesterolemia; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SI = statin-intolerant.
[a] Manufacturer's base-case analysis.[1]

Dosing Regimen for Evolocumab (Monthly Versus Every Two Weeks)

The draft product monograph for evolocumab included a 420 mg once-monthly dosing regimen in addition to the 140 mg every-two-weeks dosing regimen.[3] The economic analyses submitted by the manufacturer modelled only evolocumab dosing at 140 mg dose every two weeks for all included patient populations; the manufacturer had indicated that the 420 mg once-monthly dosing was excluded from the pharmacoeconomic analysis since an automatic dosing device for delivering the 420 mg monthly regimen was not available at the time of this review.[1] However, according to the product monograph for evolocumab, a monthly dose of 420 mg can also be delivered by administering three pre-filled auto-injectors consecutively within 30 minutes.[3] The dosing of evolocumab in the clinical studies submitted by the manufacturer for this review used both 140 mg once every two weeks and the 420 mg once-monthly dose.[5,6,11] The manufacturer considers these two dose regimens to be clinically equivalent and, although the included studies were not designed to assess differences between the two regimens, there were no obvious differences in efficacy or harms between the two.[5,6,11,17] Since both dosing regimens are approved for use in Canada, and based on the product monograph indicating that the 420 mg monthly dose can be achieved by administering three 140 mg pre-filled injections, the potential for 420 mg monthly dosing is significant.[3] Therefore, CDR conducted a reanalysis that modified the annual cost of evolocumab in the model to reflect 420 mg monthly dosing instead of the base case of 140 mg once every two weeks (Table 25). The annual drug costs for evolocumab increased from $4,500 to $6,231 when three 140 mg injections are used every month at a price per injection of $[redacted].[1]

TABLE 25: SUMMARY RESULTS FOR CADTH COMMON DRUG REVIEW REANALYSIS OF EVOLOCUMAB DOSING REGIMENS

		ICUR ($/QALY)			
	Comparators	Primary Hyperlipidemia	High-Risk Hyperlipidemia	HeFH	SI
Manufacturer's base-case analysis					
Base case: 1 injection (140 mg) every 2 weeks[a]	Medium- or high-intensity statins[b]	$100,482	$79,598	$18,457	$57,943
	Ezetimibe + medium- or high-intensity statins[c]	$151,112	$115,284	$34,744	$105,351
Scenario analysis: 3 injections (420 mg) per month	Medium- or high-intensity statins[b]	$147,498	$115,179	$32,320	$88,888
	Ezetimibe + medium- or high-intensity statins[c]	$219,924	$166,145	$55,281	$156,081
CDR multi-way sensitivity analysis					
1 injection (140 mg) every 2 weeks	Medium- or high-intensity statins[b]	$180,427	$124,922	$23,822	$95,842
	Ezetimibe + medium- or high-intensity statins[c]	$397,180	$263,929	$68,813	$172,177
3 injections (420 mg) per month	Medium- or high-intensity statins[b]	$261,180	$180,814	$43,970	$144,314
	Ezetimibe + medium- or high-intensity statins[c]	$566,984	$376,657	$106,915	$252,437

CDR = CADTH Common Drug Review; HeFH = heterozygous familial hypercholesterolemia; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SI = statin-intolerant.
[a] Manufacturer's base-case analysis.[1]
[b] Only high-intensity statins are modelled in the HeFH patient population; in SI patients, the comparator was no treatment.
[c] Ezetimibe was added to high-intensity statins in the HeFH patient population; in SI patients, the comparator was ezetimibe alone.

Price-Reduction Scenario

A price-reduction analysis was conducted on both the manufacturer's base-case analysis and the CDR multi-way sensitivity analyses when comparing evolocumab in patients with primary hyperlipidemia, high-risk patients with hyperlipidemia, and statin-intolerant patients with hyperlipidemia.
Using the manufacturer's base-case analysis and submitted confidential price of $[redacted] per 140 mg/mL pre-filled syringe (Table 26):

- In patients with primary hyperlipidemia:
  - A price reduction of approximately 50% was required for evolocumab to reach an ICUR of $39,354 per QALY when compared with medium- or high-intensity statins alone.
  - Compared with ezetimibe plus medium- or high-intensity statins, evolocumab required a price reduction of approximately 60% to reach an ICUR of $43,750 per QALY.
- In high-risk patients with hyperlipidemia:
  - A price reduction of approximately 50% was required for evolocumab to reach an ICUR of $33,335 per QALY when compared with medium- or high- intensity statins alone.
  - Compared with ezetimibe plus medium- or high-intensity statins, evolocumab required a price reduction of approximately 50% to reach an ICUR of $49,156 per QALY.

- In patients with SI:
  - A price reduction of approximately 25% was required for evolocumab to reach an ICUR or $37,825 per QALY when compared with no treatment.
  - Compared with ezetimibe alone, evolocumab required a price reduction of approximately 50% to reach an ICUR of $39,392 per QALY.

TABLE 26: CADTH COMMON DRUG REVIEW REANALYSIS PRICE REDUCTION SCENARIO — MANUFACTURER'S BASE CASE

ICURs of Submitted Drug Versus Comparator ($/QALY)						
Reduction	**Primary Hyperlipidemia**		**High-risk Hyperlipidemia**		**SI**	
	Statins alone[b]	Ezetimibe + statins[b]	Statins alone[b]	Ezetimibe + statins[b]	No treatment	Ezetimibe
Submitted price[a]	$100,482	$151,112	$79,598	$115,284	$57,943	$105,351
25%	$69,918	$106,377	$56,467	$82,220	$37,825	$72,371
50%	$39,354	$61,643	$33,335	$49,156	$17,708	$39,392
60%	$27,128	$43,750	$24,083	$35,930	$9,661	$26,200

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY= quality-adjusted life-year; SI = statin-intolerant.
[a] Manufacturer's submitted confidential price of $[redacted] per 140 mg/mL pre-filled syringe.[1]
[b] Refers to medium- or high- intensity statins.

Using the CDR multi-way sensitivity analysis and manufacturer-submitted confidential price of $[redacted] per 140 mg/mL pre-filled auto-injector (Table 27):

- In patients with primary hyperlipidemia:
  - A price reduction of approximately 60% was required for evolocumab to reach an ICUR of $54,434 per QALY when compared with medium- or high-intensity statins alone.
  - Compared with ezetimibe plus medium- or high-intensity statins, evolocumab required a price reduction of approximately 80% to reach an ICUR of $43,936 per QALY.
- In high-risk patients with hyperlipidemia:
  - A price reduction of approximately 50% was required for evolocumab to reach an ICUR of $52,252 per QALY when compared with medium- or high- intensity statins alone.
  - Compared with ezetimibe plus medium- or high-intensity statins, evolocumab required a price reduction of approximately 75% to reach an ICUR of $44,079 per QALY.
- In patients with HeFH:
  - A price reduction of approximately 25% was required for evolocumab to result in an ICUR of $44,044 per QALY when compared with ezetimibe plus high-intensity statins.
- In patients with SI:
  - A price reduction of approximately 50% was required for evolocumab to reach an ICUR of $32,818 per QALY when compared with no treatment.
  - Compared with ezetimibe alone, evolocumab required a price reduction of approximately 60% to reach an ICUR of $46,953 per QALY.

TABLE 27: CADTH COMMON DRUG REVIEW REANALYSIS PRICE REDUCTION SCENARIO — CADTH COMMON DRUG REVIEW MULTI-WAY ANALYSIS

ICURs of Submitted Drug Versus Comparator ($/QALY)								
Reduction	**Primary Hyperlipidemia**		**High-Risk Hyperlipidemia**		**HeFH**		**SI**	
	Statins alone[a]	Ezetimibe + statins[a]	Statins alone[a]	Ezetimibe + statins[a]	High-intensity statins alone	Ezetimibe + high-intensity statins	No treatment	Ezetimibe
Submitted price[b]	$180,427	$397,180	$124,922	$263,929	$23,822	$68,813	$95,842	$172,177
25%	$127,930	$286,791	$88,587	$190,646	$10,723	$44,044	$64,330	$120,000
50%	$75,432	$176,402	$52,252	$117,362	Dominant[c]	$19,274	$32,818	$67,824
60%	$54,434	$132,247	$37,718	$88,049	Dominant[c]	$9,366	$20,213	$46,953
75%	$22,935	$66,013	$15,917	$44,079	Dominant[c]	Dominant[c]	$1,306	$15,647
80%	$12,436	$43,936	$8,650	$29,422	Dominant[c]	Dominant[c]	Dominant[c]	$5,212

CDR = CADTH Common Drug Review; HeFH = heterozygous familial hypercholesterolemia; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SI = statin-intolerant.

[a] Refers to medium- or high- intensity statins.

[b] Manufacturer's submitted confidential price of $[redacted] per 140 mg/mL pre-filled syringe.[1]

[c] A dominant treatment results in additional benefits at lower costs than comparator.

REFERENCES

1. Pharmacoeconomic evaluation. In: CDR submission: Repatha, 140 mg in 1.0 mL (140 mg/mL), solution for subcutaneous injection. Company: Amgen Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Amgen Canada, Inc.; 2015.
2. Anderson TJ, Gregoire J, Hegele RA, Couture P, Mancini GB, McPherson R, et al. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol. 2013 Feb;29(2):151-67.
3. Repatha (evolocumab): Solution for subcutaneous injection, 140 mg in 1.0 mL (140 mg/mL) [product monograph]. Mississauga: Amgen Canada Inc.; 2015 Sep 10.
4. Primary Panel:, Genest J, Hegele RA, Bergeron J, Brophy J, Carpentier A, et al. Canadian Cardiovascular Society position statement on familial hypercholesterolemia. Can J Cardiol. 2014 Dec;30(12):1471-81.
5. Robinson JG, Nedergaard BS, Rogers WJ, Fialkow J, Neutel JM, Ramstad D, et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA. 2014 May 14;311(18):1870-82.
6. Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet. 2015 Jan 24;385(9965):331-40.
7. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet [Internet]. 2010 Nov 13 [cited 2015 Nov 4];376(9753):1670-81. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2988224
8. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008 Feb 12;117(6):743-53.
9. Wilson PW, D'Agostino R, Sr., Bhatt DL, Eagle K, Pencina MJ, Smith SC, et al. An international model to predict recurrent cardiovascular disease. Am J Med. 2012 Jul;125(7):695-703.
10. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab. 2012 Nov;97(11):3956-64.
11. Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol. 2014 Jun 17;63(23):2541-8.
12. Feeny D, Kaplan MS, Huguet N, McFarland BH. Comparing population health in the United States and Canada. Popul Health Metr [Internet]. 2010 [cited 2015 Nov 4];8:8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2873793
13. Matza LS, Stewart KD, Gandra SR, Delio PR, Fenster BE, Davies EW, et al. Acute and chronic impact of cardiovascular events on health state utilities. BMC Health Serv Res [Internet]. 2015 [cited 2015 Nov 4];15:173. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4408571
14. Goeree R, Lim ME, Hopkins R, Blackhouse G, Tarride JE, Xie F, et al. Prevalence, total and excess costs of diabetes and related complications in Ontario, Canada. Can J Diabetes. 2009;33(1):35-45.
15. Ontario Ministry of Health and Long-Term Care. Ontario drug benefit formulary/comparative drug index. Toronto: The Ministry; 2015.

16. Briggs AH, Claxton K, Sculpher MJ. Decision modelling for health economic evaluation. Oxford: Oxford University Press; 2006. (Handbooks in health economic evaluation series).
17. CDR submission: Repatha, 140 mg in 1.0 mL (140 mg/mL), solution for subcutaneous injection. Company: Amgen Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga: Amgen Canada Inc.; 2015 Jun.
18. Stroes E, Robinson J, Raal F, Dufour R, Sullivan D, Blagden M, et al. Clinical equivalence of evolocumab among patient subgroups in PROFICIO: a pooled analysis of 3146 patients from phase 3 studies. Poster presented at: European Society of Cardiology Congress. 2015; Aug 29 - Sep 2; London.
19. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making. 2011 Nov;31(6):800-4.
20. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. Med Decis Making [Internet]. 2006 Jul [cited 2015 Sep 11];26(4):410-20. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2634296
21. Comparative Effectiveness Public Advisory Council. PCSK9 inhibitors for treatment of high cholesterol: Effectiveness, value, and value-based price benchmarks: Draft report [Internet]. Boston (MA): Institute for Clinical and Economic Review; 2015 Sep 8. [cited 2015 Sep 9]. Available from: http://cepac.icer-review.org/wp-content/uploads/2015/04/PCSK9_Draft_Report_0908151.pdf
22. Department of Health and Community Services. Newfoundland and Labrador Drug Products Database [Internet]. St. John's (NL): Government of Newfoundland and Labrador; 2015 [cited 2015 Nov 4]. Available from: http://www.health.gov.nl.ca/health/prescription/newformulary.asp
23. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015 Apr 16;372(16):1500-9.
24. Statistics Canada [Internet]. Ottawa (ON): Government of Canada. Life tables, Canada, provinces and territories; 2013 [cited 2015 Sep 1]. Available from: http://www5.statcan.gc.ca/olc-cel/olc.action?objId=84-537-X&objType=2&lang=en&limit=0
25. Statistics Canada [Internet]. Ottawa (ON): Government of Canada. Table 102-0529 - Deaths, by cause, Chapter IX: Diseases of the circulatory system (I00 to I99), age group and sex, Canada; 2014 Jan 28 [cited 2015 Sep 1]. Available from: http://www5.statcan.gc.ca/cansim/a05?lang=eng&id=1020529
26. Mittmann N, Seung SJ, Hill MD, Phillips SJ, Hachinski V, Cote R, et al. Impact of disability status on ischemic stroke costs in Canada in the first year. Can J Neurol Sci. 2012 Nov;39(6):793-800.
27. Smolderen KG, Bell A, Lei Y, Cohen EA, Steg PG, Bhatt DL, et al. One-year costs associated with cardiovascular disease in Canada: Insights from the REduction of Atherothrombosis for Continued Health (REACH) registry. Can J Cardiol. 2010 Oct [cited 2015 Nov 4];26(8):297-305. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2954538
28. Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease [Internet]. London: National Collaborating Centre for Primary Care and Royal College if General Practitioners; 2008. [cited 2015 Nov 4]. (NICE guidelines [CG67]). Available from: https://www.nice.org.uk/guidance/cg67
29. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ [Internet]. 2003 Jun 28 [cited 2015 Nov 4];326(7404):1423. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC162260