CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

EVOLOCUMAB (REPATHA — AMGEN CANADA INC)
Indication: As an adjunct to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C)

For Clinical Atherosclerotic Cardiovascular Disease:

RECOMMENDATION:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that evolocumab be reimbursed as an adjunct to diet and maximally tolerated statin therapy in adult patients for clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C), if the following criterion and condition are met:

Criterion:

- Patients meet the inclusion criteria for the FOURIER trial:
  - Established cardiovascular disease and are at high risk for future events,
  - LDL-C≥1.8 mmol/L or non-HDL-C≥2.6 mmol/L, and
  - Taking maximally tolerated dose of statins.

Condition:

- Price reduction of at least 90%.

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Reasons for the Recommendation:

1. In one double-blind, placebo-controlled, randomized clinical trial enrolling patients with ASCVD receiving optimized statin therapy (FOURIER, n=27,564), a composite outcome of CV death, MI, stroke, UA, or revascularization was experienced by 9.8% of patients taking evolocumab and 11.3% of patients taking placebo over a median follow-up period of 26 months (hazard ratio 0.85 [95% confidence interval, 0.79 - 0.92]).
2. CDR evaluation of a cost utility analysis in a population of ASCVD patients using information related to clinically important outcomes observed in the FOURIER trial concluded that the ICUR for evolocumab plus SOC vs SOC alone is $1,007,961 per QALY, and the ICUR for evolocumab plus SOC vs. ezetimibe plus SOC is $1,478,417 per QALY. Based on this reanalysis, a price reduction over 90% would be required for the ICUR for evolocumab to fall to $50,000 per QALY when compared to statins alone or ezetimibe plus statins.

Of Note:

- CDEC noted that the incremental benefit of adding evolocumab to existing therapy is small and largely limited to a reduction in myocardial infarction. Death and death due to cardiovascular causes were not significantly different between groups.
- CDEC noted a lack of evidence related to longer term outcomes beyond 26 months, the median follow-up period in the FOURIER trial, including both durability of clinical effectiveness and potential harms. This limitation is of particular importance due to the novel molecular nature of evolocumab, and evidence of development of neutralizing antibodies to one other PCSK9 inhibitor.
- CDEC noted that there is limited evidence to evaluate the efficacy and cost effectiveness of evolocumab relative to other PCSK9 inhibitors. An ITC submitted by the manufacturer is of limited utility due to use of surrogate outcomes when clinical outcomes are available, as well as lack of outcome data related to harms. The FOURIER trial failed to demonstrate a strong correlation between LDL-C levels and clinical outcomes, making extrapolation from other trials or to other populations based on LDL-C levels unreliable.

Discussion Points:

- There remains uncertainty as to the use of evolocumab in relation to the use of ezetimibe. As most patients in FOURIER were not on ezetimibe, the role of triple therapy with evolocumab, ezetimibe, and a statin is uncertain. Analyses are also unavailable to determine which patients may be candidates for combination therapy with a statin and ezetimibe versus a statin and evolocumab.
- Although the pharmacoeconomic model submitted by the manufacturer was not optimized to leverage data from the FOURIER trial, that trial provides direct evidence of the impact of treatment with evolocumab on meaningful clinical cardiovascular outcomes, and was available at the time of the CDR review. Direct evidence related to cardiovascular outcomes was considered by CDEC to be more credible and reliable than the extrapolation of benefits from the included meta-analysis and the LAPLACE-2 trial.
- While risk profiles and event rates may differ between clinical trials and real world settings, it is challenging to identify patients outside of clinical trials who are likely to meet all of the indications for evolocumab, in particular the requirement for using a maximally tolerated statin dose, since the tolerability is rarely recorded in observational data. Furthermore, CDR re-analysis of the pharmacoeconomic model indicated that cost-effectiveness ratios were only marginally lower if only the baseline LDL-C levels were changed, indicating that the main driver of cost-effectiveness was efficacy of evolocumab, rather than baseline risks or event rates; CDEC considered that such efficacy is best estimated from the FOURIER study.

Background:

This resubmission for evolocumab is for the previously reviewed Health Canada indication of adjunct to diet and maximally tolerated statin therapy in adult patients with clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). Evolocumab is a monoclonal antibody directed against pro-protein convertase subtilisin/kexin type 9 (PCSK9), and therefore belongs to the class of drugs referred to as PCSK9 inhibitors. Evolocumab is administered as a subcutaneous injection, either 420 mg once monthly or 140 mg twice monthly.

Submission History:

Evolocumab was previously reviewed for the treatment of patients with heterozygous familial hypercholesterolemia (HeFH), and patients with clinical atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of low-density lipoprotein-cholesterol (LDL-C). For the former indication it received a positive listing recommendation, while for the latter it received a recommendation of 'do not list'.

The original CDR review of evolocumab included four double-blind (DB) RCTs: LAPLACE-2, RUTHERFORD-2, DESCARTES, and GAUSS-2. DESCARTES was a 52-week study, while the other studies were 12 weeks in duration. The studies ranged in size from 307 to 1899 participants, and patients with established ASCVD made up <35% of the population across the included studies. Across studies, patients were either on background statin therapy or ezetimibe. The studies were not powered to assess clinical outcomes, there were few cardiovascular events across studies, and no statistically significant differences in any study between evolocumab and comparison groups were observed for clinical outcomes. At the submitted price, CDR reanalysis of the manufacturer's PE model suggested that evolocumab was cost-effective when combined with high intensity statins in patients with HeFH who are unable to meet target LDL-C levels with currently available therapies (ICUR of $23 822 to $68 813 per QALY when compared with high intensity statins alone or ezetimibe plus high intensity statins). Therefore, CDEC recommended reimbursing evolocumab in patients with HeFH who require additional lowering of LDL-C and are receiving optimally tolerated standard of care. However due to the lack of evidence that evolocumab could reduce risk of CV events in patients with clinical ASCVD and the small proportion (<35%) of patients with established ASCVD across the included studies, CDEC recommended evolocumab not be reimbursed in this population.

This resubmission is based on the effects of evolocumab in patients with established ASCVD, from two studies not previously reviewed by CDR and post hoc subgroup analyses of patients with ASCVD from studies completed at the time of the original CDR review of evolocumab. The two new studies not available at the time of the original CDR review are GLAGOV and the recently completed FOURIER trial. Of the two, FOURIER had a much higher proportion of participants with established ASCVD (81% of

participants in FOURIER had a prior myocardial infarction versus 35% in GLAGOV). FOURIER was not part of the formal resubmission package from the manufacturer; however, results from FOURIER were recently published and this study met the inclusion criteria for this systematic review

Summary of CDEC Considerations:

The Committee considered the following information prepared by the Common Drug Review: a systematic review of RCTs of evolocumab and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience treating patients with atherosclerotic cardiovascular disease, and patient group-submitted information about outcomes and issues important to patients and caregivers who are affected by atherosclerosis.

Patient Input Information

Input was received from one patient group, the Cardiac Health Foundation of Canada (CHFC). The information provided by the CHFC was gathered through an online survey targeted to patients living with atherosclerosis and their caregivers (to which there were 55 responses) and through one telephone interview. The following is a summary of key input from the perspective of the patient group:

- Controlling the progression of the disease was a major concern for most patients and caregivers. Many said they were worried about what could happen and some said they were depressed. Fatigue was the prime physical symptom identified by patients as affecting their daily lives.
- All patients reported they had taken rosuvastatin or atorvastatin. Most patients rated these medications as effective or somewhat effective. A small proportion, however, said they had to discontinue taking a statin because of sore muscles, weakness and cramping—problems also experienced by some patients who continued taking a statin. Some of these patients had to reduce their dose of the statin they were taking.
- Two of the three patients who had taken evolocumab reported that it had been quite effective in reducing their cholesterol levels and improving their energy levels and that it has caused "limited to no side effects." The other said it had reduced cholesterol levels but had caused soreness in the arm.
- Patients who had not taken evolocumab said they expected it to "lower their cholesterol with minimal side effects." Some clearly regarded evolocumab as an alternative to statin therapy rather than as an adjunct to it.

Clinical Trials

The systematic review included two multicentre, manufacturer-sponsored double-blind randomized controlled trials of patients with atherosclerotic cardiovascular disease (ASCVD). FOURIER randomized 27564 patients in a 1:1 manner to either evolocumab (140 mg every 2 weeks or 420 mg monthly, according to patient preference) or placebo. FOURIER was an event-driven study and had a median follow up of 26 months. The population featured patients with 'clinically evident' ASCVD (either a previous MI, non-hemorrhagic stroke, or symptomatic peripheral artery disease) as well as additional risk factors. Patients had a fasting LDL-C above 1.8 mmol/L or non-HDL-C above 2.6 mmol/L while on optimized lipid lowering therapy (defined as at least atorvastatin 20 mg or equivalent, plus or minus ezetimibe). The design of FOURIER addressed two key limitations of the original CDR submission, enrolling a population with established ASCVD, and with sufficient power to assess hard clinical outcomes such as cardiovascular morbidity and mortality. GLAGOV randomized 970 patients with ASCVD, in a 1:1 manner, to either evolocumab 420 mg monthly or placebo over 78 weeks. The proportion of participants withdrawing from FOURIER was relatively low (<1% in each group), while in GLAGOV 3.3% of evolocumab-treated and 4.1% of placebo-treated participants withdrew from the study.

Key limitations were that neither study compared evolocumab to alirocumab, the other approved PCSK9 inhibitor, and neither study was likely of sufficient duration to assess long-term harms. While FOURIER was designed to assess clinical outcomes, a limitation of GLAGOV is that its primary outcome (change in percent atheroma volume) is a surrogate, with no established minimum clinically important difference.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: major adverse cardiovascular events, mortality (all-cause and cardiovascular-related) and harms. The primary outcome in FOURIER was a composite of major cardiovascular events (CV deaths, MI, stroke, hospitalization for UA, or coronary revascularization), while the primary outcome in GLAGOV was the change from baseline in percent atheroma volume. Quality of life was not evaluated in either study. Major adverse cardiovascular events are clearly of importance and a key concern of patients with ASCVD, as noted in their input to CDR.

Efficacy

In FOURIER, evolocumab demonstrated superiority over placebo for both the primary and key secondary (composite of cardiovascular death, myocardial infarction, or stroke) outcomes. For both the primary (proportion of participants experiencing a primary outcome event with evolocumab: 9.8% versus placebo: 11.3%) and key secondary (evolocumab: 5.9% versus placebo: 7.4%) outcomes, the effect size was 1.5%, with a HR [95% confidence interval] of 0.85 [0.79, 0.92], p<0.001 for the primary endpoint and 0.80 [0.73, 0.88], p<0.001 for the key secondary endpoint. There was no difference in all-cause or cardiovascular mortality between evolocumab and placebo. Evolocumab subjects experienced a large reduction in LDL-C versus placebo, consistent with that seen in the trials included in the original submission to CDR. Therefore, the large reduction in LDL-C resulted in relatively small reductions in major cardiovascular events and no reduction in risk of death. The relatively short follow-up may have contributed to the lack of observed treatment effect for mortality and the relatively small treatment effect for the primary and key secondary composite outcomes. FOURIER was originally planned to last approximately five years, but the required number of key secondary endpoint events was reached earlier than expected, and therefore as noted above, the trial ended after a median follow-up of only 26 months.

In GLAGOV, evolocumab demonstrated superiority over placebo for the primary outcome; however, the clinical significance of the reported change in percent atheroma volume is unknown, as there is no established minimum clinically important difference. GLAGOV was not designed to assess clinical outcomes.

Harms (Safety and Tolerability)

- In FOURIER and in GLAGOV, there were similar serious adverse events with evolocumab compared with placebo.
- Overall adverse events were similar with evolocumab compared with placebo.
- Notable harms were similar between evolocumab and placebo, including neurocognitive events, which were a concern with PCSK9 inhibition that emerged in the previous review of evolocumab, and muscle-related events, which are a concern of patients on statin therapy. The follow up in FOURIER and GLAGOV was likely not of sufficient duration to assess long term safety.

Cost and Cost-Effectiveness

Evolocumab is indicated for use in adult patients with ASCVD who require additional lowering of LDL-C, as an adjunct to diet and maximally tolerated statin therapy. The dosage form is 1 mL solution (140 mg/mL evolocumab) in a single-use prefilled auto-injector which is intended for subcutaneous patient self-administration. At the submitted price of $279.36 per 140 mg dose and the recommended dose of 140 mg every 2 weeks, the annual cost of evolocumab is $7,263.

The manufacturer submitted a cost utility analysis (CUA) comparing evolocumab plus medium- or high-intensity statins with medium- or high-intensity statins alone (standard of care, SOC) in patients with known ASCVD. Baseline CV risk was based on Clinical Practice Research Database (CPRD), a retrospective observational cohort study in multiple UK cohorts, and LDL-C levels from the study population (LAPLACE-2). Similar to the previous submission of evolocumab, the treatment effects were assessed by combining treatment efficacy in terms of (absolute) LDL-C lowering from the evolocumab trial (LAPLACE-2) and the results from a meta-analysis of 26 randomized clinical trials of statins which estimated the impact of absolute reductions in LDL-C levels on CV events (Baigent 2010). The analyses were conducted from the perspective of a Canadian publicly-funded health care system assuming a lifetime time horizon (40 years). The manufacturer reported an incremental cost-utility ratio (ICUR) of $112,196 per

quality-adjusted life year (QALY) when compared to SOC in the base case analysis. The scenario analysis that compared evolocumab to ezetimibe as add-on to SOC resulted in an ICUR of $158,855 per QALY.

CDR identified the following key limitations with the manufacturer's economic submission:

- In the model, the manufacturer based their economic model on surrogate outcomes to predict long term CV risk and mortality while trial data which captured clinically important outcomes was available (FOURIER).
- Baseline risk was derived from the baseline characteristics of patients in the LAPLACE-2 trial who experienced a prior CV event, thereby affecting the generalizability of the results to the requested indication (ASCVD patients).
- The rate ratios for cardiovascular events associated with LDL-C reduction from evolocumab 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).
- In the base case analysis, the manufacturer assumed a lifetime time horizon and duration of treatment up to 40 years. It is not yet established that clinical efficacy persists over a patient lifetime given the relatively short duration of available trials.
- The health state utilities in the model were based on values from an industry-funded trial in the UK despite the availability of Canadian utility data for CV events.

In addressing the identified limitations, CDR considered a population with characteristics similar to the GLAGOV study population (similar to FOURIER) with relative risks (RRs) of clinically important outcomes observed in FOURIER replacing the surrogate outcomes. In the CDR analysis, at the recommended dose of 140 mg every 2 weeks, the incremental cost utility ratio (ICUR) for evolocumab + SOC vs. SOC is $1,007,961 per QALY. Using the same assumptions as above, the ICUR for evolocumab + SOC vs. ezetimibe + SOC is $1,478,417 per QALY. CDR re-analyses showed that results were sensitive to evolocumab efficacy when based on clinically important outcomes from trial data rather than on surrogate outcomes.

A price reduction over 90% would be required for the ICUR for evolocumab to fall to $50,000 per QALY when compared to statins alone or ezetimibe plus statins.

CDEC Members:

July 19, 2017 Meeting

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

Regrets:

None

Conflicts of Interest:

One CDEC member did not participate due to considerations of conflict of interest.

November 15, 2017 Meeting

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets:

None

Conflicts of Interest:

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