



Canadian Agency for  
Drugs and Technologies  
in Health

# COMMON DRUG REVIEW

## CADTH CANADIAN DRUG EXPERT REVIEW COMMITTEE FINAL RECOMMENDATION

### EVOLOCUMAB

(Repatha — Amgen Canada Inc.)

Indication: Primary Hyperlipidemia

#### For Heterozygous Familial Hypercholesterolemia

##### **Recommendation:**

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

##### **Clinical Criteria:**

- Patient has a confirmed diagnosis of HeFH.
- Patient is unable to reach LDL-C target (i.e., LDL-C < 2.0 mmol/L).
- Patient is currently receiving optimally tolerated standard of care (typically statins with or without ezetimibe).

##### **Condition:**

- The drug plan cost of a dosage regimen of 420 mg of evolocumab once per month should not exceed the drug plan cost of a dosage regimen of 140 mg of evolocumab every two weeks.

##### **Reasons for the Recommendation:**

1. Four double-blind randomized controlled trials (RCTs) (LAPLACE-2, RUTHERFORD-2, DESCARTES, and GAUSS-2) demonstrated that evolocumab (140 mg every two weeks or 420 mg once per month) was statistically significantly superior to placebo, with or without concurrent ezetimibe and background statin therapy, at lowering LDL-C levels.
2. At the submitted price (██████████), reanalyses of the manufacturer's pharmacoeconomic model conducted by the CADTH Common Drug Review (CDR) suggest that evolocumab, in combination with high-intensity statins, is associated with an incremental cost-utility ratio (ICUR) of \$23,822 to \$68,813 per quality-adjusted life-year (QALY) when compared with high-intensity statins alone or ezetimibe plus high-intensity statins. Therefore, CDEC considered evolocumab to be a cost-effective treatment option for patients with HeFH who are unable to meet target LDL-C levels with currently available therapies.

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3. Compared with a dose of 140 mg every two weeks, the use of evolocumab at a dose of 420 mg once per month is associated with increased costs and no additional improvement in clinical outcomes.

### **For Clinical Atherosclerotic Cardiovascular Disease**

#### **Recommendation:**

CDEC recommends that evolocumab not be listed as an adjunct to diet and maximally tolerated statin therapy in adult patients with clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of LDL-C.

#### **Reasons for the Recommendation:**

1. Due to the short duration of the available clinical trials, there is insufficient evidence to evaluate the clinical benefit of evolocumab for reducing the risk of cardiovascular events in patients with clinical atherosclerotic CVD.
2. The manufacturer requested that evolocumab be listed for use in 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; however, these patients represented a relatively small proportion (< 35%) of the patients studied in the clinical trials. In addition, there were no pre-specified subgroup analyses conducted specifically for this patient population.

#### **Of Note:**

- Evolocumab is also indicated as an adjunct to diet and other LDL-lowering therapies (e.g., 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. The manufacturer of evolocumab did not request reimbursement for this indication; therefore, it was not included in this CDR review.
- Evolocumab has a novel mechanism of action and the included studies, both RCTs and extension studies, do not provide adequate characterization of the long-term safety profile.

#### **Background:**

Evolocumab is a fully human monoclonal antibody that binds to human proprotein convertase subtilisin/kexin type 9 (PCSK9). Evolocumab has the following Health Canada–approved indications: as an adjunct to diet and maximally tolerated statin therapy in adult patients with HeFH or clinical atherosclerotic CVD, who require additional lowering of LDL-C; and as an adjunct to diet and other LDL-lowering therapies in adult patients and adolescent patients aged 12 years and over with HoFH who require additional lowering of LDL-C. The current CDR submission is focused on the use evolocumab in patients with HeFH or CVD who require additional lowering of LDL-C.

Evolocumab is available in 140 mg/mL pre-filled syringes or pens and is administered by subcutaneous (SC) injection. The recommended dose is either evolocumab 140 mg every two weeks (EVO 140 q.2w.) or evolocumab 420 mg once monthly (EVO 420 q.m.).

### Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies of evolocumab, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients with hypercholesterolemia.

### Patient Input Information

Two patient groups, Heart and Stroke Foundation and Familial Hypercholesterolemia Canada Patient Network, responded to the CDR call for patient input. Information was obtained through online surveys, interviews, focus groups, closed discussion groups, online forums, and literature searches. The following is a summary of information provided by the patient groups:

- Patients with familial hypercholesterolemia are at an increased risk of developing CVD and experiencing events such as strokes and myocardial infarctions. Patients reported a range of emotional symptoms associated with the condition, including feelings of stress, anxiety, fear, and frustration with not being able to attain or maintain their target cholesterol levels.
- Patients reported experience with oral therapies, such as statins and ezetimibe, as well as plasma apheresis. Side effects associated with the oral treatments included muscle pain, shortness of breath, fatigue, joint and chest pain, headaches, muscle weakness, tenderness or spasms, sleep issues, dry mouth or altered taste, gastrointestinal issues, and skin reactions. Apheresis treatments were noted as being inconvenient and required absences from work. Their effectiveness was also reported as often waning over time.
- Patients noted there remains an unmet need for the treatment of familial hypercholesterolemia, as many patients fail to meet cholesterol targets and continue to experience cardiovascular events with existing treatments. In addition, patients would prefer treatments with fewer side effects and more convenient administration than those that are currently available. The need for SC administration was not noted as a major concern for the patient groups.

### Clinical Trials

The CDR systematic review included the following four double-blind RCTs:

- LAPLACE-2 (N = 1,899) initially randomized patients to background regimens of various statins (i.e., atorvastatin 10 mg or 80 mg, rosuvastatin 5 mg or 40 mg, and simvastatin 40 mg). Once stabilized, patients were then randomized 2:2:1:1:1:1 to evolocumab (140 mg or 420 mg), matching placebo, or matching placebo plus ezetimibe 10 mg daily (only patients on atorvastatin received ezetimibe) for a period of 12 weeks.
- RUTHERFORD-2 (N = 331) was a placebo-controlled study with HeFH patients randomized 2:2:1:1 to evolocumab (140 mg or 420 mg) or matching placebo for 12 weeks.
- DESCARTES (N = 905) was also a placebo-controlled study (randomized 2:1, evolocumab to placebo), with all evolocumab patients receiving the 420 mg dose, on a variety of different background therapies (atorvastatin 10 mg/day, atorvastatin 80 mg/day, atorvastatin 80 mg/day plus ezetimibe, or diet alone) over 52 weeks.
- GAUSS-2 (N = 307) was an ezetimibe-controlled study conducted in patients with statin intolerance. Patients were randomized (2:2:1:1) to either evolocumab (140 mg or 420 mg) or to matching placebo plus ezetimibe 10 mg daily, over a treatment period of 12 weeks.

**Outcomes**

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Percentage change from baseline in LDL-C.
- Cardiovascular events and death — these events were adjudicated by an independent committee and included: death by any cause, cardiovascular death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack, and hospitalization for heart failure.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary outcome for all studies was the percentage change from baseline in LDL-C.

**Efficacy**

- There were few adjudicated cardiovascular events, no more than 2% of patients in any group, across the included trials, and no clear difference in proportions between groups.
- In GAUSS-2, the per cent reduction in LDL-C was statistically significantly greater in the evolocumab groups compared with the ezetimibe groups. The least squares mean differences in per cent reduction in LDL-C were:
  - EVO 140 q.2w. versus ezetimibe: -38.06 (95% CI, -43.73 to -32.39) at week 10/12 and -36.90 (95% CI, -42.26 to -31.55) at week 12
  - EVO 420 q.m. versus ezetimibe: -37.55 (95% CI, -42.16 to -32.94) at week 10/12 and -38.69 (95% CI, -43.06 to -34.32) at week 12.
- In RUTHERFORD-2, both evolocumab groups were superior to the placebo groups for reducing LDL-C at 10/12 weeks and 12 weeks. The least squares mean differences in per cent reduction in LDL-C were:
  - EVO 140 q.2w. versus placebo: -60.2% (-65.8 to -54.5) at weeks 10/12 and -59.2% (95% CI, -65.1 to -53.4) at week 12
  - EVO 420 q.m. versus placebo: -65.6% (-71.3 to -59.8) at weeks 10/12 and -61.3% (95% CI, -69.0 to -53.6) at week 12.
- In LAPLACE-2, the per cent reduction in LDL-C was statistically significantly greater in the evolocumab groups compared with the ezetimibe and placebo groups, irrespective of background statin usage. The least squares mean differences in per cent reduction in LDL-C at 12 weeks were:
  - Atorvastatin 80 mg background therapy:
    - EVO 140 q.2w. versus ezetimibe/placebo q.2w.: -47.20 (95% CI, -57.54 to -36.86)
    - EVO 420 q.m. versus ezetimibe/placebo q.m.: -38.88 (95% CI, -48.21 to -29.56)
    - EVO 140 q.2w. versus placebo q.2w.: -76.29 (95% CI, -86.87 to -65.72)
    - EVO 420 q.m. versus placebo q.m.: -70.51 (95% CI, -79.81 to -61.20).
  - Atorvastatin 10 mg background therapy:
    - EVO 140 q.2w. versus ezetimibe/placebo q.2w.: -47.20 (95% CI, -57.54 to -36.86)
    - EVO 420 q.m. versus ezetimibe/placebo q.m.: -38.88 (95% CI, -48.21 to -29.56)
    - EVO 140 q.2w. versus placebo q.2w.: -76.29 (95% CI, -86.87 to -65.72)
    - EVO 420 q.m. versus placebo q.m.: -70.51 (95% CI, -79.81 to -61.20).
  - Combined analysis (any statin background therapy):
    - EVO 140 q.2w. versus placebo q.2w.: -70.79 (95% CI, -74.13 to -67.44)
    - EVO 420 q.m. versus placebo q.m.: -62.18 (95% CI, -65.93 to -58.43).
- In DESCARTES, after 52 weeks there was a statistically significant reduction in LDL-C in the EVO 420 q.m. group compared with the placebo group (-56.97%; 95% CI, -61.08 to -52.85).

**Harms (Safety and Tolerability)**

- The most commonly reported adverse events across the included studies were nasopharyngitis, upper respiratory tract infections, influenza, myalgia, and headache. The proportions of patients who experienced at least one adverse event were:
  - 12 weeks: EVO 140 q.2w., 39% to 61%; EVO 420 q.m., 35% to 71%; ezetimibe/placebo q.2w., 43% to 69%; ezetimibe/placebo q.m., 38% to 77%; placebo q.2w., 41% to 43%; placebo q.m., 36% to 55%
  - 52 weeks: EVO 420 q.m., 75% and placebo q.m., 74%.
- Serious adverse events were relatively rare across the included studies. The proportions of patients who experienced at least one serious adverse event were:
  - 12 weeks: EVO 140 q.2w., 3% to 5%; EVO 420 q.m., 1% to 4%; ezetimibe/placebo q.2w., 1% to 2%; ezetimibe/placebo q.m., 1% to 6%; placebo q.2w., 3% to 4%; placebo q.m., 3% to 5%
  - 52 weeks: EVO 420 q.m., 6% and placebo q.m., 4%.
- There were very few discontinuations due to adverse events in LAPLACE-2, RUTHERFORD-2, and DESCARTES. In GAUSS-2, the proportion of patients discontinuing due to adverse events was greater than in the other studies and there were numerical differences in the proportion of patients between groups. The highest proportion of patients discontinuing was in the EZE/PLA q.m. group (18%) and the lowest percentage was in the EVO 140 q.2w. group (6%). The proportions of patients who withdrew as a result of adverse events were:
  - 12 weeks: EVO 140 q.2w., 0% to 6%; EVO 420 q.m., 0% to 11%; ezetimibe/placebo q.2w., 3% to 8%; ezetimibe/placebo q.m., 1% to 18%; placebo q.2w., 0% to 2%; placebo q.m., 0% to 4%
  - 52 weeks: EVO 420 q.m., 2% and placebo q.m., 1%.

**Cost and Cost-Effectiveness**

The manufacturer submitted a cost-utility analysis of evolocumab in four patient populations:

- as add-on to medium- or high-intensity statins in patients with primary hyperlipidemia and/or mixed dyslipidemia, compared with medium- or high-intensity statins alone or in combination with ezetimibe
- as add-on to medium- or high-intensity statins in high-risk patients with non-familial hyperlipidemia with a prior cardiovascular event, compared with medium- or high-intensity statins alone or in combination with ezetimibe
- in patients with HeFH as add-on to high-intensity statins, compared to high-intensity statins alone or in combination with ezetimibe
- in patients who are statin intolerant, compared with ezetimibe or no treatment.

The treatment effects were assessed by combining treatment efficacy in terms of (absolute) LDL-C lowering from LAPLACE-2 and RUTHERFORD-2, and the results from a meta-analysis of 26 RCTs of statins that estimated the impact of absolute reductions in LDL-C levels on cardiovascular events (Baigent 2010). The analyses were conducted from the perspective of a Canadian publicly funded health care system, assuming a lifetime horizon (up to 120 years of age). Evolocumab was costed as 140 mg every two weeks at a price of [REDACTED]. In all analyses, the manufacturer reported that treatment with evolocumab resulted in greater QALYs at additional cost when compared with other treatments, resulting in ICURs for evolocumab of 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.

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

- In the model, the manufacturer used clinical effect estimates for ezetimibe from GAUSS-2, which compared two doses of evolocumab (140 mg or 420 mg) with matching placebo plus ezetimibe 10 mg per day. In the submitted model, ezetimibe was assessed as an add-on to ongoing statin therapy, but patients in GAUSS-2 were not using statins; hence, the modelled treatment effect of ezetimibe added on to ongoing statin therapy may have been underestimated. Efficacy estimates for ezetimibe added on to statins could have been obtained from LAPLACE-2, which included an ezetimibe plus statins group.
- The model used rate ratios for cardiovascular events that were derived from Baigent (2010) and are not from consistent populations. While estimates for acute coronary syndrome and ischemic stroke were from the "more versus less statin" studies (identified as being the most representative of the evaluated population), the estimates for coronary heart disease and fatal ischemic stroke were from the overall populations, rather than the "more versus less statin" group.
- In the base-case analysis, the manufacturer assumed a lifetime time horizon up to the age of 120 years, and duration of treatment for up to 75 years, which are likely too long considering that patients enter the model at 59 years of age, and considering the lack of long-term evidence available.
- The health state utilities in the model were based on values from an industry-funded trial by Matza et al. (2015) despite the availability of Canadian utility data for cardiovascular events. However, the model results were not sensitive to this variation.
- The calculation of the annual costs of statins in the model did not correspond to calculations made based on publicly available prices for statins in Canada. However, the model results were not sensitive to this correction.

In addressing the identified limitations, CDR found that the model results were sensitive to the effect of LDL-C reduction on death due to coronary heart disease, ezetimibe efficacy on lowering LDL-C, and changes to the time horizon. The following results were obtained once these limitations were addressed:

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

### Other Discussion Points:

CDEC noted the following:

- Evolocumab is relatively costly compared with alternative treatment options. CDEC noted that, for the majority of patients included in the manufacturer's listing request, a substantial price reduction (50% to 80%) would be required for the drug to be considered a cost-effective option compared with statins alone or ezetimibe plus statins.

- CADTH should consider conducting a therapeutic review of cholesterol-lowering drugs to evaluate the comparative clinical benefit of PCSK9 inhibitors.

### Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- The product monograph states that the effect of evolocumab on cardiovascular morbidity and mortality has not been determined.
- The longer-term safety and efficacy profile of evolocumab requires further evaluation.
- There are limited clinical data for use of evolocumab in patients with prior cardiovascular events. The manufacturer is currently conducting a large, double-blind, placebo-controlled, RCT to evaluate the impact of evolocumab in combination with statin therapy on major cardiovascular events in patients with CVD (FOURIER; N = 27,564).

### CDEC Members:

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

### January 20, 2016 Meeting

#### Regrets:

None

#### Conflicts of Interest:

None

#### About this Document:

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

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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