CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

ICOSAPENT ETHYL (VASCEPA — HLS THERAPEUTICS INC.)
Indication: Prevention of cardiovascular events in statin-treated patients.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that icosapent ethyl be reimbursed to reduce the risk of cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or hospitalization for unstable angina) in statin-treated patients with elevated triglycerides, if the following conditions are met.

Conditions for Reimbursement
Initiation Criteria
1. Patients aged 45 years and older with established cardiovascular disease (secondary prevention).
2. Patients must have a fasting triglyceride of 1.7 mmol/L or greater and lower than 5.6 mmol/L at baseline, measured within the preceding three months before starting treatment with icosapent ethyl.
3. Patients must have a low-density lipoprotein cholesterol greater than 1.0 mmol/L and lower than 2.6 mmol/L at baseline and be receiving a maximally tolerated statin dose, targeted to achieve a low-density lipoprotein cholesterol lower than 2 mmol/L, for a minimum of four weeks.

Prescribing Conditions
Icosapent ethyl should only be prescribed with a statin.

Pricing Conditions
A reduction in price.

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ICOSAPENT ETHYL (VASCEPA — HLS Therapeutics Inc.)

Indication: Prevention of cardiovascular (CV) events in statin-treated patients.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that icosapent ethyl be reimbursed to reduce the risk of CV events (CV death, non-fatal myocardial infarction [MI], non-fatal stroke, coronary revascularization, or hospitalization for unstable angina) statin-treated patients with elevated triglycerides (TGs), if the following conditions are met.

Conditions for Reimbursement

Initiation Criteria

1. Patients aged 45 years or older with established cardiovascular disease (CVD) (secondary prevention population).
2. Patients must have a fasting TG of 1.7 mmol/L or greater and lower than 5.6 mmol/L at baseline, measured within the preceding three months before starting treatment with icosapent ethyl.
3. Patients must have a low-density lipoprotein cholesterol (LDL-c) greater than 1.0 mmol/L and lower than 2.6 mmol/L at baseline and be receiving a maximally tolerated statin dose, targeted to achieve an LDL-c lower than 2 mmol/L, for a minimum of four weeks.

Prescribing Conditions

Icosapent ethyl should be prescribed in conjunction with a statin.

Pricing Conditions

A reduction in price.

Reasons for the Recommendation

1. One double-blind, randomized controlled trial (RCT) (REDUCE-IT; N = 8,179) demonstrated a statistically significant reduction in major CV events (composite of CV mortality, non-fatal MI, non-fatal stroke, coronary revascularization, and hospitalization for unstable angina) in patients with established CVD (secondary prevention), a fasting TG of 1.7 or greater and lower than 5.6 mmol/L, and an LDL-c greater than 1.0 and lower than 2.6 mmol/L at baseline**,** who were treated with icosapent ethyl 4 g per day added to statin therapy compared with those treated with statin therapy plus placebo (absolute risk reduction of 6.2%; hazard ratio [HR] = 0.726; 95% confidence interval [CI], 0.650 to 0.810).
2. CDEC noted that there was significant uncertainty about the efficacy of icosapent ethyl 4 g per day added to statin therapy, compared with statin plus placebo therapy, to support a listing recommendation that included patients with diabetes and at least one other CV risk factor (primary prevention). The uncertainty arises from both the efficacy of icosapent ethyl for the desired outcomes and the proportion of patients in the general population who would meet criteria for primary prevention.
    2.1. The pre-specified subgroup analysis in the REDUCE-IT study that compared the primary and secondary prevention groups met the criterion for concluding that the treatment effect was different across subgroups (P = 0.14, which was lower than the pre-specified P value threshold of 0.15). The HR for major CV events (composite of CV mortality, non-fatal MI, non-fatal stroke, coronary revascularization, and hospitalization for unstable angina) for primary prevention patients treated with icosapent ethyl was 0.876, with a 95% CI that included no efficacy (0.700 to 1.095).
    2.2. The overall estimate of treatment effect was essentially a weighted average of treatment effects across subgroups; the REDUCE-IT study restricted the size of the primary prevention group to be no greater than 30% of the entire study population. In practice, the proportion of patients meeting criteria for primary prevention are likely to be larger than the number meeting criteria for secondary prevention. As such, the efficacy in the overall Canadian population remains uncertain and is likely to be considerably lower than the effect estimated in the REDUCE-IT trial. CDEC noted that the absolute risk reduction in the primary prevention subgroup was considerably smaller than in the secondary prevention subgroup (1.4% versus 6.2%, respectively). Therefore, CDEC had concerns about the long-term balance between benefits and harms when icosapent ethyl is used for primary prevention (the REDUCE-IT trial did not report details regarding onset, duration, or severity of harms and their necessary management by subgroup).
3. The sponsor-submitted price of icosapent ethyl is $2.45 per 1 g capsule, with an annual treatment cost of $3,577 per patient. CADTH reanalysis of the sponsor-provided economic model estimated the incremental cost-utility ratio (ICUR) to be $105,053

per quality-adjusted life-year (QALY) for icosapent ethyl plus statin compared with statin therapy alone for the full population studied in the REDUCE-IT trial (i.e., primary and secondary prevention). A price reduction of at least 43% would be required to achieve an ICUR of $50,000 per QALY. CADTH was unable to conduct stratified analyses to evaluate the cost-effectiveness in the secondary prevention subgroup due to a lack of clinical data for each of the individual CV outcomes stratified by risk. The potential cost-effectiveness of icosapent ethyl in the secondary prevention subgroup remains uncertain.

Implementation Considerations

- Reimbursement of icosapent ethyl may be associated with a large budget impact due to the expected population size that would be eligible for treatment. To manage its potential impact on drug plan budgets, drug plans should consider setting pricing arrangements when implementing the reimbursement of icosapent ethyl.

Discussion Points

- CDEC noted that the results of the REDUCE-IT trial have limited generalizability because the patients enrolled in the study were a selective subset of the patient population for whom this drug is likely to be prescribed in practice.
  - A total of 57% of screened patients were ineligible for enrolment into the trial. This ineligibility raises concerns that icosapent ethyl may be considered in practice for many patients who do not meet the narrow inclusion criteria of the REDUCE-IT trial. Additionally, patients enrolled in the REDUCE-IT study were restricted to those with fasting TGs of 1.7 mmol/L (150 mg/dL) or greater and lower than 5.6 mmol/L (500 mg/dL), and who had LDL-c levels greater than 1.0 mmol/L (40 mg/dL) and lower than 2.6 mmol/L (100 mg/dL). CDEC received clinician expert input that patients with lipid values outside these ranges may be prescribed icosapent ethyl in Canada. Therefore, in clinical practice, icosapent ethyl may be prescribed to a broader non-studied patient population with TG and/or LDL-c concentrations outside the aforementioned REDUCE-IT trial limits.
  - Despite statin therapy targeted to reduce LDL-c lower than 2.0 mmol/L, only 30% of patients enrolled in REDUCE-IT were receiving high-dose statin therapy and, according to the clinical experts consulted, this percentage is lower than expected within current Canadian clinical practice.
  - The true mechanism(s) of action of icosapent ethyl have yet to be defined. A reduction in CV outcomes was observed in the REDUCE-IT trial across a range of levels of reduction in fasting TG concentrations. As such, demonstration of reduced fasting TG blood levels with icosapent ethyl should not be used to determine whether icosapent ethyl should be continued or discontinued.
- A second RCT, ANCHOR (N = 702), demonstrated that icosapent ethyl 4 g orally per day reduced TGs, LDL-c, and high-sensitivity C-reactive protein from baseline when compared with placebo in a population of adults already receiving a stable dose of statin therapy (with or without ezetimibe) and at high risk for CVD. ANCHOR did not examine the effects of icosapent ethyl on clinical outcomes and therefore could not be used to verify the results observed in REDUCE-IT. The purported mechanisms through which icosapent ethyl might reduce CV events are numerous and not necessarily directly related to reduced concentrations of triglycerides or other important lipids.

Background

Icosapent ethyl (Vascepa) is a highly purified ethyl ester of eicosapentaenoic acid, with a Health Canada–approved indication to reduce the risk of CV events (CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or hospitalization for unstable angina) in statin-treated patients with elevated triglycerides, who are at high risk of CV events due to established CVD or diabetes and have at least one other CV risk factor. The drug underwent an expedited (priority) review with Health Canada. The sponsor's reimbursement request is the same as the indication. Icosapent ethyl is supplied as a 1 g liquid-filled soft gelatin capsule for oral administration with a recommended total dosage of 4 g per day (two 1 g capsules twice a day).

Submission History

Icosapent ethyl has not been previously evaluated by CADTH.

Summary of Evidence Considered by CDEC

CDEC considered the following information prepared by the CADTH Common Drug Review: a systematic review of RCTs of icosapent ethyl and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience in treating patients with CVD.

Summary of Patient Input

No patient group–submitted information about outcomes and issues important to patients was available for this submission.

Clinical Trials

Two RCTs met the criteria for inclusion into the CADTH systematic review. The REDUCE-IT study, conducted in 11 countries, with a median follow-up of 4.9 years (up to 6.2 years) included 8,179 patients aged 45 years or older with established CV risk, and those aged 50 years or older with diabetes in combination with one additional risk factor for CVD. Patients were required to have baseline fasting TGs of 1.7 mmol/L (150 mg/dL) or greater and lower than 5.6 mmol/L (500 mg/dL), an LDL-c of greater than 1.0 mmol/L (40 mg/dL) and lower than 2.6 mmol/L (100 mg/dL), and be receiving stable doses of statins. The study evaluated 4 g per day orally of icosapent ethyl versus placebo. The primary outcome assessed was the time from randomization to the first occurrence of any of the composite outcome events of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, and unstable angina requiring hospitalization. Secondary outcomes were evaluated in a hierarchical fashion and included a key secondary composite end point of time from randomization to any of CV death, non-fatal MI, or non-fatal stroke; a composite of CV death or non-fatal MI; fatal or non-fatal MI; emergency or urgent revascularization; CV death; hospitalization for unstable angina; fatal or non-fatal stroke; a composite of total mortality, non-fatal MI (including silent MI), or non-fatal stroke; and total mortality.

ANCHOR was the second included study; it was conducted in 97 centres across the US and had 12 weeks of follow-up. It included 702 patients aged 18 years or older with fasting TG levels of 2.3 mmol/L or greater and 5.6 mmol/L or lower, who were receiving a stable dose of statin therapy (with or without ezetimibe), and who were at high risk for CVD. This study included three treatment groups: placebo, icosapent ethyl 2 g daily, and icosapent ethyl 4 g daily. Only the icosapent ethyl 4 g daily dosage group was included because that is the Health Canada–recommended dosage. The study evaluated the percent change in TG levels from baseline to week 12 as the primary outcome. CV events and other clinically important outcomes were not assessed. Secondary end points included the percent change in non–high-density lipoprotein cholesterol, LDL-c, apolipoprotein B, very low-density lipoprotein, and lipoprotein-associated phospholipase A2 from baseline to week 12.

Approximately 10% of patients in both studies were lost to follow-up and 30% had a drug interruption for more than 30 days, but there were no differences between groups in these numbers; hence, the risk of bias from attrition was judged as moderate. Neither study was adequately designed for analyzing subgroups. Generalizability of the results from REDUCE-IT is a concern given that the benefits and harms were derived from a single RCT, and only 43% of patients who underwent screening were randomized to treatment groups in the study. There is also uncertainty regarding the generalizability of the distribution of statin intensity at baseline in the REDUCE-IT trial. ANCHOR was a relatively small, short-term study that focused on evaluating changes in blood lipid profiles instead of clinical outcomes; therefore, this study is supportive in demonstrating the effect of icosapent ethyl on reduction in triglycerides but does little to elucidate the clinical value the drug adds in the target population. No studies for indirect treatment comparisons were available.

Outcomes

Outcomes were defined a priori in the CADTH Common Drug Review systematic review protocol. Of these, the committee discussed the following:

- mortality (including CV mortality and all-cause mortality)
- morbidity (including non-fatal CV events; hospitalizations due to heart failure, arrhythmia, or unstable angina; and revascularization of any kind)
- health-related quality of life
- changes in TGs, LDL-c, high-density lipoprotein cholesterol, and C-reactive protein levels.

Efficacy

In the REDUCE-IT study, 17% of patients treated with icosapent ethyl 4 g versus 22% of patients in the placebo group had at least one of the events of the composite outcome of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, and unstable angina (HR = 0.75; 95% CI = 0.68 to 0.83). Icosapent ethyl 4 g also reduced CV mortality (HR = 0.80; 95% CI, 0.65 to 0.98), non-fatal MI (HR = 0.69; 95% CI, 0.59 to 0.82), non-fatal stroke (HR = 0.70; 95% CI, 0.53 to 0.93), hospitalizations due to unstable angina (HR = 0.67; 95% CI, 0.53 to 0.86), and need for coronary revascularization (HR = 0.66; 95% CI, 0.58 to 0.75) compared with placebo. Icosapent ethyl did not demonstrate benefit versus placebo on overall mortality (HR = 0.87; 95% CI, 0.74 to 1.02), hospitalization due to heart failure (HR = 0.97; 95% CI, 0.77 to 1.22), or arrhythmia (HR = 1.21; 95% CI, 0.97 to 1.49).

Subgroups of interest for the CADTH clinical review were baseline CVD risk (established CVD or at high risk for CVD) and baseline diabetes (diabetes or no diabetes). The results of the subgroup analyses of the primary outcome in REDUCE-IT were similar to those for the full population: icosapent ethyl reduced the risk of the composite outcome relative to placebo. The results did not find statistically significant differential effects between categories within each of these subgroups. However, as mentioned, limitations with the subgroup analyses preclude drawing definitive conclusions.

Data from the REDUCE-IT and ANCHOR trials indicated that icosapent reduced the levels of TG, LDL-c, and high-sensitivity C-reactive protein from baseline when compared with placebo.

Harms (Safety)

Adverse events, serious adverse events, and withdrawals due to adverse events occurred at similar frequencies between the icosapent ethyl and placebo groups in both studies. Atrial fibrillation occurred more frequently in the icosapent ethyl group compared with the placebo group (5.3% versus 3.9%, respectively) in the REDUCE-IT study but not in the ANCHOR study (0% versus less than 1%, respectively). Peripheral edema occurred more frequently in the icosapent ethyl group than in the placebo group in both the REDUCE-IT study (6.5% versus 5.0%, respectively) and the ANCHOR study (1.3% versus 0.9%, respectively). Serious adverse bleeding events occurred in 2.7% of patients in the icosapent ethyl group and 2.1% in the placebo group in the REDUCE-IT trial; there were no fatal bleeding events in either group. There were no differences between the icosapent ethyl group and the placebo group in the proportion of adjudicated hemorrhagic stroke. Also, a higher percentage of patients in the icosapent ethyl group reported constipation compared with those in the placebo group (5.4% versus 3.6%, respectively).

Of all notable harms, only diarrhea was slightly increased in the placebo group (11%) versus the intervention group (9%), although this was only present in the REDUCE-IT study. The other adverse events reported in both studies occurred in less than 3% of patients and were similar between groups.

Cost and Cost-Effectiveness

Icosapent ethyl is available in 1 g capsules with a recommended daily dose of 4 g, taken as two separate 2 g doses twice daily. At the sponsor-submitted price of $2.45 per 1 g capsule, the annual cost of treatment is $3,577 per patient.

The sponsor submitted a cost-utility analysis based on a Markov state-transition model that assessed the costs and QALYs of treatment with icosapent ethyl in addition to statin therapy compared with statin therapy alone. The analysis was conducted over a 20-year time horizon from the Canadian public health care payer perspective with costs and QALYs discounted at 1.5%. All patients started in the model in the “cardiovascular event (CVE)-free” health state and remained in this state until experiencing either a non-fatal or fatal CVE (including CVE-related death, non-fatal MI, non-fatal stroke, coronary revascularization, and unstable angina). Survivors of a non-fatal CVE moved to a “post non-fatal CVE” health state, where they could experience subsequent non-fatal CVE or fatal CVE. Data from the statins-alone group of the REDUCE-IT trial was extrapolated using parametric survival methods and was used to inform the model transition from the CVE-free state to the post non-fatal CVE state for patients receiving statin therapy alone. Relative treatment effects and costs for icosapent ethyl plus statins were applied for the first five years of the model time horizon, with relative treatment effects based on the HRs derived from the REDUCE-IT trial for each CV event included in the submitted model. In the sponsor’s base-case analysis, icosapent ethyl plus statin therapy was associated with higher costs ($12,523) and more QALYs (0.29) than statin therapy alone, resulting in an ICUR of $42,797 per QALY gained.

CADTH identified the following key limitations with the sponsor's submitted economic analysis:

- The CADTH clinical review noted that the population studied in the REDUCE-IT trial was highly selective, which makes generalizability of the study results uncertain.
- The 20-year time horizon was insufficient to assess the impacts of treatment for a chronic condition.
- Icosapent ethyl was assumed to only be used for the first five years, at which point all patients would discontinue treatment. Clinical expert feedback received during the review suggested that patients responding to icosapent ethyl would likely continue treatment and experience benefits throughout their lifetime. The sponsor's assumption underestimated both the treatment impact and the costs associated with icosapent ethyl.
- Several utility values related to post non-fatal CV events were incorrect. In most cases, the utility values in the model were lower than observed in the published literature. As the frequency for CV events was higher in patients receiving statin therapy alone, this biased health outcomes in favour of icosapent ethyl.
- Due to the model structure and the lack of clinical data available, the cost-effectiveness of icosapent ethyl by risk stratum remains unknown.

CADTH undertook a reanalysis that included adopting a lifetime time horizon, applying drug acquisition costs and benefits for icosapent ethyl over a lifetime, and revising several utility values for post non-fatal CV events.

Based on CADTH reanalysis, the ICUR for icosapent ethyl plus statins was $105,053 per QALY gained when compared with statins alone. The results were primarily driven by drug acquisition costs, with a price reduction of 43% required for icosapent ethyl plus statin therapy to be cost-effective at a willingness-to-pay threshold of $50,000 per QALY. The cost-effectiveness of icosapent ethyl in a broader clinical population beyond what has been studied in the REDUCE-IT trial is unknown.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

December 11, 2019 Meeting (Initial)

Regrets

None

Conflicts of Interest

None

May 20, 2020 Meeting (Reconsideration; Deferred to June 17, 2020)

Regrets

None

Conflicts of Interest

None

June 17, 2020 Meeting (Reconsideration)

Regrets

None

Conflicts of Interest

None