CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

ICOSAPENT ETHYL (VASCEPA)

(HLS Therapeutics Inc.)

Indication: Prevention of cardiovascular events in statin-treated patients

Service Line:	CADTH Common Drug Review
Version:	Final
Publication Date:	August 2020
Report Length:	29 Pages

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

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Abbreviations

CDR	CADTH Common Drug Review
CI	confidence interval
CVD	cardiovascular disease
CVE	cardiovascular event
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
HR	hazard ratio
ICUR	incremental cost-utility ratio
MACE	major adverse cardiovascular event
NICE	National Institute for Health and Care Excellence
QALY	quality-adjusted life-year
SE	standard error

Table 1: Summary of the Sponsor's Economic Submission

Drug product	Icosapent ethyl (Vascepa)
Study question	In comparison to statin treatment alone, what is the cost-utility of the addition of icosapent ethyl for the reduction of ischemic cardiovascular events in statin-treated patients with elevated triglycerides and other risk factors such as established cardiovascular disease (CVD) or being at high risk of CVD from the perspective of a publicly funded health care payer?
Type of economic evaluation	Cost-utility analysis
Target population	Statin-treated adult patients with elevated triglycerides and other risk factors such as established CVD or being at high risk of CVD
Treatment	4 g icosapent ethyl per day, plus statin treatment
Outcome	Quality-adjusted life-year (QALY)
Comparator	Statin treatment alone
Perspective	Canadian public health care payer
Time horizon	20 years
Results for base case	Incremental cost-utility ratio (ICUR) = $42,797 per QALY gained
Key limitations	• A 20-year time horizon was adopted in the sponsor's base case. As this is a treatment for a chronic condition, a lifetime time horizon would be most appropriate. • In the sponsor's base case, it was assumed that icosapent ethyl would only be used for five years, at which point it would be discontinued. According to feedback from clinical experts consulted by CADTH, 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 (to a greater degree) associated with icosapent ethyl. • Several utility values related to post–non-fatal cardiovascular events were incorrect. In most cases, the utility values in the model were lower than anticipated. As the frequency for cardiovascular events was higher in patients receiving statin treatment alone, this biased outcomes in favour of icosapent ethyl. • The clinical efficacy of icosapent ethyl plus statin therapy may vary by risk stratum, leading to differences in cost-effectiveness of icosapent ethyl. However, because of the model structure and the lack of clinical data available, the cost-effectiveness of icosapent ethyl by risk stratum remains unknown. • The CADTH clinical review noted the population studied in the REDUCE-IT trial was highly selective. The cost-effectiveness of icosapent ethyl in the entire population likely to receive this drug is unknown. • Feedback from the clinical experts consulted by CADTH indicated that niacin, fibrates, and fish oils containing EPA (the active ingredient in icosapent ethyl), with or without DHA, are currently used off-label in clinical practice in addition to the maximum tolerated dose of statin therapy for the same indication as icosapent ethyl. These were not included in the model, and the cost-effectiveness of icosapent ethyl compared to these treatments remains unknown.

CDR estimate(s)	CADTH conducted reanalyses that included the following: adopting a lifetime time horizon; applying drug acquisition costs and benefits for icosapent ethyl for the full duration of the model time horizon; and revising several utility values for post–non-fatal cardiovascular events • The revisions resulted in a CADTH base-case ICUR of $105,053 per QALY gained for icosapent ethyl plus statins versus statins alone. • A price reduction of 43% would be required for the ICUR to be below $50,000 per QALY gained.

CDR = CADTH Common Drug Review; CVD = cardiovascular disease; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Drug	Icosapent ethyl (Vascepa)
Indication	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, who are at high risk of cardiovascular events due to: • established cardiovascular disease, or • diabetes, and at least one other cardiovascular risk factor
Reimbursement request	As per indication
Dosage form(s) and route of administration)/strength(s)	1 g capsules for oral administration
NOC date	December 30, 2019
Sponsor	HLS Therapeutics Inc.

Executive Summary

Background

Icosapent ethyl (Vascepa) is indicated for reduction of cardiovascular events (CVEs; e.g., cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or hospitalization for unstable angina) in statin-treated patients with elevated triglycerides and established cardiovascular disease (CVD), or with diabetes and at least one other cardiovascular risk factor.[1] Icosapent ethyl is available in 1 g capsules with a recommended daily dose of 4 g, taken as two 1 g capsules twice daily.[1] At the sponsor-submitted price of $2.45 per 1 g capsule, the annual cost of treatment is $3,577 per patient. The sponsor's reimbursement request was in accordance with its Health Canada indication.[2]

The sponsor submitted a cost-utility analysis based on a Markov state-transition model that assessed the costs and quality-adjusted life-years (QALYs) of treatment with icosapent ethyl in addition to statin therapy compared to statin therapy alone.[3] 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%.[3] Patients entered the model in the "CVE-free" health state and remained in that state until experiencing either a non-fatal or fatal CVE (including CVE-related death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, and unstable angina). Survivors of a non-fatal CVE would enter and remain in a "post–non-fatal CVE" health state in the following model cycles, where they could experience subsequent non-fatal CVEs or fatal CVEs. A baseline risk of non-cardiovascular death was applied in the model. Data from the statins-alone arm of the REDUCE-IT trial, extrapolated using parametric survival methods, was used to inform the baseline model transition from the CVE-free state to the post–non-fatal CVE state. 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 hazard ratios (HRs) derived from the REDUCE-IT trial comparing time to first primary end point for each CVE included in the model in patients treated with icosapent ethyl plus statins compared to statins alone.[4]

In the sponsor's base case, icosapent ethyl plus statin therapy was associated with higher costs ($12,523) and more QALYs (0.29) than statin therapy alone, resulting in an incremental cost-utility ratio (ICUR) of $42,797 per QALY gained.

Summary of Identified Limitations and Key Results

CADTH identified several key limitations with the manufacturer's economic submission.

CADTH noted that the 20-year time horizon does not align with the latest guidance from the CADTH Guidelines for the Economic Evaluation of Health Technologies.[5] A lifetime time horizon would be more appropriate to capture all of the potential differences in costs and outcomes between treatments for this chronic condition.

The sponsor assumed icosapent ethyl would be discontinued after five years of treatment and that treatment effects would apply only during the first five years of the model time horizon, aligning with the study methodology of the REDUCE-IT trial. Feedback from the clinical experts consulted by CADTH indicated that, in clinical practice, patients would likely remain on treatment beyond five years. The magnitude of the clinical effectiveness of icosapent ethyl beyond the trial period is unclear, although clinical experts consulted by CADTH anticipated benefits would continue to be accrued. These assumptions, as applied in the sponsor's base case, underestimated the costs and QALYs associated with icosapent ethyl.

CADTH reviewers noted several incorrect utility values for post–non-fatal CVEs. When assessing the sponsor-cited UK National Institute for Health and Care Excellence (NICE) health technology assessment,[6] the values for post–non-fatal stroke, post–non-fatal myocardial infarction, and post–unstable angina were incorrect, mainly overestimating the utility impact of such events.[6] A related issue with utilities involved the assumption made for the utility value for post-revascularization. In the sponsor's base case, it was assumed patients would have the same utility post-revascularization as they would have in the acute revascularization phase. On the contrary, the study that informed the utility values in the NICE health technology assessment suggests that the utility impact post-revascularization would return to levels similar to that before revascularization.[7] Given that fewer patients on icosapent ethyl experienced CVEs, these limitations together biased results in its favour by overestimating the impact on quality of life.

The clinical evidence suggests that the efficacy of icosapent ethyl may vary by risk stratum (i.e., primary and secondary prevention cohorts). The CADTH clinical report noted that, while there may be a difference in effect for the two subgroups, the clinical study was underpowered to detect whether such a difference was statistically significant. CADTH was unable to conduct stratified analyses by subgroup due to a lack of clinical data for each of the individual cardiovascular outcomes stratified by risk. The potential cost-effectiveness of icosapent ethyl may differ between the primary and secondary prevention cohort, although the magnitude to which the ICUR may change is unknown. Furthermore, the CADTH clinical review noted that the population studied in the REDUCE-IT trial was highly selective. According to the clinical experts consulted on this review, many patients who were considered screening failures in the trial would likely be prescribed icosapent ethyl in clinical practice. The cost-effectiveness of icosapent ethyl in the entire population likely to receive this drug is unknown.

Not all comparators of interest were included in the sponsor's analysis. As noted above, the sponsor's analysis did not include any active comparators in addition to statin therapy, which

was justified based on the literature indicating there is no evidence of benefit with their use. Feedback from the clinical experts consulted by CADTH on this review indicated active comparators (i.e., niacin, fibrates, and fish oils containing eicosapentaenoic acid [EPA]) are currently used in clinical practice off-label, although there is limited evidence of benefit with their use. As a result, they would be potentially relevant comparators and, given their absence, the cost-effectiveness of icosapent ethyl in comparison to these treatments remains uncertain.

CADTH undertook a reanalysis that included the following: incorporating a lifetime time horizon; applying drug acquisition costs and benefits over the full duration of the model time horizon; and revising utility values for certain post–non-fatal CVE health states. In the CADTH reanalysis, icosapent ethyl plus statin therapy was associated with higher total costs ($117,105 versus $67,713) and QALYs (12.03 versus 11.56) than statin therapy alone, resulting in an ICUR of $105,053 per QALY gained.

Conclusions

In statin-treated adult patients with elevated triglycerides and other risk factors or who are at high risk of CVD, the CADTH base-case reanalysis estimated that icosapent ethyl plus statin therapy resulted in increased costs and greater QALYs than statin therapy alone, resulting in an ICUR of $105,053 per QALY gained. 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 compared to relevant comparators currently used in clinical practice, in addition to statin therapy, or in a broader clinical population beyond what has been studied in the REDUCE-IT trial, is unknown. Cost-effectiveness may further differ among patients classified by different risk strata (i.e., primary prevention or secondary prevention) within the indication.

Information on the Pharmacoeconomic Submission

Summary of the Sponsor's Pharmacoeconomic Submission

The sponsor submitted a cost-utility analysis comparing icosapent ethyl plus statin therapy to statin therapy alone for the reduction of CVEs (i.e., CVE-related death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, and unstable angina) in patients 45 years of age or older with established CVD or 50 years of age or older with diabetes mellitus and other CVD risk factors, with elevated triglycerides (1.53 to 5.63 mmol/L or 135 to 499 mg/dL) and cholesterol (1.0 to 2.6 mmol/L or 40 to 100 mg/dL) on stable statin therapy.[1,3] No other comparators were considered, based on the sponsor's assertion that limited efficacy was observed with other therapies that aim to reduce triglyceride levels when administered in addition to statin therapy. The analysis was conducted from the Canadian public health care payer perspective with yearly cycles over a 20-year time horizon. A discount rate of 1.5% was applied to costs and QALYs.[3] Baseline characteristics (e.g., gender, age, and distribution of statin intensity) upon model entry were based primarily on data from the REDUCE-IT trial.[4] Statin regimens falling under each intensity category were defined by the 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on Treatment of Blood and Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.[8] Additionally, a proportion of patients were assumed to be receiving 10 mg ezetimibe based on data from the REDUCE-IT trial.

A Markov state-transition model was submitted to reflect the natural history of disease and the effects of treatment, consisting of the following five health states: CVE-free, death from fatal cardiovascular causes, non-fatal CVE, post–non-fatal CVE, and death from other (non-CVE) causes. Patients entered the model in the CVE-free state and were at risk of fatal or non-fatal CVE. Patients experiencing a fatal CVE transitioned to death from fatal cardiovascular causes, while patients experiencing a non-fatal CVE were further categorized to one of the following events: non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or hospitalization for unstable angina,[3] and in the following model cycle moved into the post–non-fatal CVE state. While in the post–non-fatal CVE state, patients were at risk of subsequent fatal or non-fatal CVEs. In all alive health states, patients had a baseline risk of non-cardiovascular death (i.e., thereby entering the "death from other [non-CVE] causes" health state). Both death states were absorbing states in which patients remained upon entry (Figure 1).

Natural history, in the form of transition probabilities, was based on parametric models for each of the individually included CVEs from the statin-only arm of the REDUCE-IT trial.[4] Treatment efficacy for icosapent ethyl plus statin therapy was also informed by the REDUCE-IT trial. Transition probabilities for icosapent ethyl plus statin therapy were calculated by applying individual HRs for each of the primary CVEs to the transition probabilities expected for statin-only therapy. Treatment efficacy was applied only to the first five years of the model's time horizon. To estimate the occurrence of secondary major adverse CVEs (MACE) for patients in the post-CVE state, a probability of any CVE event was applied, based on the data from the REDUCE-IT trial, with the type of event assigned based on the distribution of secondary MACE events reported in the REDUCE-IT trial (Figure 2). Treatment-specific transition probabilities for secondary MACE events were applied for only the first five years in the model, after which the model assumed event rates were equal between groups and patients would not experience any subsequent CVE events.

All-cause mortality was obtained from Statistics Canada life tables,[9] and, beyond year five of the model's time horizon, patients with a history of CVE were assumed to be at an increased risk of death.[10,11] Adverse event risks were derived from the REDUCE-IT trial.[4]

Health state utility values were obtained from the published literature. A baseline value of 0.762 was used to reflect the fact that patients had existing CVD, or diabetes and a high risk of CVD, at baseline. The utility value for acute or post-CVE was calculated by multiplying the utility values associated with the specific event by the baseline utility value noted previously. Disutilities for adverse events were also included based on values identified in the published literature.[12-15] Drug costs for icosapent ethyl were obtained from the sponsor, while costs of statin therapy and ezetimibe were obtained from the Ontario Drug Benefit e-Formulary.[16] No acquisition costs for icosapent ethyl were applied after the first five years in the model.[4] Costs related to CVE and adverse events were obtained from a combination of the published literature and the Ontario Case Costing Initiative,[17] while disease management resource use was obtained from a combination of clinical practice guidelines[8] and clinical expert opinion, and costed according to the Ontario Schedule of Benefits.[18]

Sponsor's Base Case

In the sponsor's base case, icosapent ethyl plus statin therapy was $12,523 more expensive and produced more QALYs (0.29), resulting in an ICUR of $42,797 per QALY gained compared to statin therapy alone over 20 years (Table 2). The majority of the cost difference was driven by drug costs ($16,764), followed by the cost to manage the first CVE, whereas the QALY difference was driven primarily by the fewer number of patients experiencing coronary revascularization (Table 12). Icosapent ethyl plus statin therapy had a 70.4% probability of being cost-effective at a willingness-to-pay threshold of $50,000 per QALY.

Table 2: Summary of Results of the Sponsor's Base Case

	Total costs ($)	Incremental cost of icosapent ethyl ($)	Total QALYs	Incremental QALYs of icosapent ethyl	Incremental cost per QALY ($)
Statin therapy alone	42,341		9.58		
Icosapent ethyl plus statin therapy	54,864	12,523	9.88	0.29	42,797

QALY = quality-adjusted life-year.

Source: Sponsor's submission.[3]

Summary of Sponsor's Sensitivity Analyses

The sponsor evaluated several alternative assumptions using scenario analyses conducted probabilistically. The model results were most sensitive to its time horizon. Specifically, in adopting a lifetime time horizon, the incremental costs decreased and QALYs increased for icosapent ethyl with statins versus statin therapy alone, resulting in an ICUR of $32,925.

Additionally, several deterministic sensitivity analyses were conducted to test the sensitivity of individual parameter inputs on the overall economic findings. The model was found to be most sensitive to patients' starting age, the HR for cardiovascular death, and the statistical parameters around cardiovascular death (mean and standard deviation).

Limitations of Sponsor's Submission

- **Inappropriate time horizon:** The sponsor considered a 20-year time horizon in its base case, citing previous CADTH Common Drug Review (CDR) reviews and recommendations for medications indicated for the treatment of high cholesterol. While CADTH recognizes prior reviews and the time horizons considered appropriate in these reviews, they were conducted before the latest edition of the CADTH Guidelines for the Economic Evaluation of Health Technologies.[5] The latest guidelines note that the time horizon should be long enough to capture all potential differences in costs and outcomes between the therapies under consideration. Thus, the appropriate time horizon for this chronic condition would capture the patient's lifetime. The use of a shorter time horizon in the sponsor's base case likely biased results against icosapent ethyl, as shown by the results of a scenario analysis conducted by the sponsor using a lifetime time horizon. A lifetime time horizon was used in the CADTH base case, and a 20-year time horizon was used in a scenario analysis.
- **Duration of treatment effects and costs of icosapent ethyl have been underestimated:** Given a lack of comparative efficacy data beyond five years, the sponsor assumed treatment effects would apply only in the first five years of the model's time horizon. In accordance with this, they also assumed that the cost of therapy would only be applied during the first five years of the model (i.e., no drug acquisition costs for icosapent ethyl beyond the first five years). In effect, the assumption made suggests all patients would discontinue icosapent ethyl after five years. Feedback from clinical experts consulted by CADTH indicated patients would be prescribed icosapent ethyl beyond the five-year time horizon that has been studied in the trial, as patients can be expected to continue to benefit from treatment. Further to this, there is no specific mention in their anticipated product monograph restricting treatment duration to five years. This assumption underestimated the costs and QALYs associated with icosapent ethyl. As drug costs are a key driver of cost differences in the model and the model is, to a greater degree, more sensitive to this parameter, the sponsor's approach would bias results in favour of icosapent ethyl. CADTH addressed this limitation by extending the application of treatment efficacy (with respect to the primary CVE event) and costs for the entirety of the time horizon, beyond the initial five years. In light of limited long-term evidence, experts suggested it would be reasonable to assume that treatment benefits would remain constant with those observed during the trial period. As treatment-specific transition probabilities for secondary MACE events were available only for the first five years, CADTH continued to apply an increased mortality risk associated with CV events beyond the first five years in the model.
- **Incorrect post–non-fatal CVE utility values used:** Upon review of the literature cited as the source of utility values for several non-fatal CVEs, several discrepancies were identified. The NICE report cited by the sponsor as the source for utility values related to revascularization did not include any values specific to revascularization, as this was not a specific clinical event in its model.[6] It appears that the sponsor selected the values for stable angina, with an assumption that there was no difference in utility values from the acute phase to the post-revascularization phase. Of note, the NICE report referenced by the sponsor as the source of this utility value cited another health technology assessment on the use of statins for prevention of coronary events.[7] In that study, revascularization was a possible clinical event in its economic evaluation, and the authors of that study assumed that post-revascularization patients would return to their baseline utility value.[7] Given the differences in revascularization rates between treatments, the assumption that

the utility values for acute and post-revascularization are identical favours icosapent ethyl because it estimates fewer QALYs on statin-only therapy. This assumption overestimates the impact of revascularization events on utility, biasing results in favour of icosapent ethyl. A utility multiplier of one for post-revascularization was used in the CADTH base case. A lower value was tested in a scenario analysis, recognizing that some studies have suggested that post-revascularization does not achieve the same utility as return to baseline values, albeit not worse than acute revascularization.[19]

Additionally, the NICE review cited by the sponsor as the source of utility values for post–non-fatal stroke, post–non-fatal myocardial infarction (MI), and post–unstable angina reported the utility values for these events as 0.628, 0.880, and 0.880, respectively, whereas the sponsor's model used 0.683, 0.808, and 0.808, respectively.[6] The correct utility values from the NICE review were used in the CADTH base case.

- **Efficacy of icosapent ethyl may vary by risk stratum:** Table 2 of the REDUCE-IT trial publication[4] shows HRs of the primary trial end point for various pre-specified subgroups. One such subgroup is a stratification by risk category, which included the following two risk strata: secondary prevention (established CVD) and primary prevention (diabetes with one other risk factor). For the composite primary clinical end point, Bhatt et al. identified an HR of 0.73 (95% confidence interval [CI], 0.65 to 0.81) in the secondary-prevention subgroup and an HR of 0.88 (95% CI, 0.70 to 1.10) in the primary-prevention subgroup, indicating that the efficacy of icosapent ethyl may vary for these subgroups.[4] The CADTH clinical review noted that, while there may be a difference of effect for the two subgroups, the REDUCE-IT trial was underpowered to detect whether such a difference was statistically significant. The clinical experts consulted by CADTH indicated that, if more patients had been included in the trials, it may have been reasonable to observe a clinically meaningful difference in effect between risk strata. If the clinical effectiveness of icosapent ethyl does differ by risk subgroups, the use of a combined HR reflecting the full population in the economic analysis would not allow comprehensive understanding of the differential cost-effectiveness across these distinct subgroups. CADTH was unable to conduct stratified analyses by subgroup due to a lack clinical data (HRs) for each of the individual cardiovascular outcomes stratified by risk strata. The potential cost-effectiveness of icosapent ethyl may differ between the primary- and secondary-prevention cohort, although the magnitude to which the ICUR may change is unknown.
- **Selective patient population:** The comparative efficacy data incorporated in the model were based on the REDUCE-IT trial. As noted in the CADTH clinical review, the population studied was highly selective. A large number of patients were considered screening failures due to the study's exclusion criteria (e.g., triglyceride level below 2.3 mmol/L [200 mg/dL] or above 5.6 mmol/L [500 mg/dL], congestive heart failure, active liver disease, or a planned coronary surgery or intervention). According to clinical experts consulted on this review, it is reasonable to expect that, in real clinical practice, many of the patients considered screening failures in the trial may be treated with icosapent ethyl. The clinical experts consulted on this review further noted that the available clinical studies provide limited evidence on the drug's efficacy in patients younger than 50 years and older than 70 years. The generalizability of the economic results may therefore be restricted to the specific population enrolled in the REDUCE-IT study.
- **Not all comparators of interest were included:** The sponsor did not include any regimen that included both statin therapy and an additional active treatment in the model, based on literature indicating no evidence of benefit with other agents currently prescribed for the same indication as icosapent ethyl. Icosapent ethyl is a highly purified version of EPA. Feedback from the clinical experts consulted by CADTH indicated that niacin,

fibrates, and fish oils containing EPA (the active ingredient in icosapent ethyl), with or without docosahexaenoic acid (DHA), are currently used off-label in clinical practice in addition to the maximum tolerated dose of statin therapy. Although clinical experts consulted by CADTH noted that there is limited evidence of clinical benefit of these agents, which is in line with the sponsor's rationale for their exclusion, icosapent ethyl would be expected to displace these alternative treatments. The cost-effectiveness of icosapent ethyl compared to these agents in statin-treated patients with elevated triglycerides and established CVD or those at high risk of CVD remains unknown.

CADTH Common Drug Review Reanalyses

CADTH undertook the following reanalyses to address the limitations of the model:

- applying a lifetime time horizon (i.e., 46 years)
- assuming icosapent ethyl would be used for the entire time horizon, meaning that treatment effects and drug acquisition costs were applied for the model's full time horizon
- adjusting utility values to reflect appropriate values from the cited literature:[6]
  - post–non-fatal stroke: 0.628 (standard error [SE] 0.040)
  - post–unstable angina: 0.880 (SE 0.018)
  - post–non-fatal myocardial infarction: 0.880 (SE 0.018)
  - post-acute coronary revascularization multiplier of 1.0 (SE 0).[7]

Results of the reanalyses are presented in Table 3. Compared with the sponsor's base case, the CADTH base case resulted in an increase in total costs and total QALYs for both icosapent ethyl plus statins (costs $117,105; QALYs 12.03) and statin therapy alone (costs $67,713; QALYs 11.56), due primarily to the increased time horizon and the assumption that patients would remain on treatment over their lifetime. Incremental costs ($49,392) increased to a greater degree than incremental QALYs (0.47), resulting in an ICUR of $105,053 per additional QALY gained for icosapent ethyl plus statins compared to statin therapy alone.

Table 3: Summary of Results of the CADTH Base Case

	Description	Manufacturer's base-case value	CDR value	Incremental cost of icosapent ethyl ($)	Incremental QALYs of icosapent ethyl	Incremental cost per QALY ($)
	Sponsor base case	**Reference**		12,523	0.29	42,797
1	Time horizon	20-year time horizon	Lifetime	11,997	0.36	32,902
2	Duration of icosapent ethyl efficacy and costs applied	5 years	Lifetime	43,464	0.42	104,098
3	Utility value multipliers post-cardiovascular events	• Post–non-fatal stroke: 0.683 (SE 0.040) • Post–unstable angina: 0.808 (SE 0.018) • Post–non-fatal myocardial	• Post–non-fatal stroke: 0.628 (SE 0.040) • Post–unstable angina: 0.880 (SE 0.018) • Post–non-fatal myocardial	12,575	0.23	55,641

	Description	Manufacturer's base-case value	CDR value	Incremental cost of icosapent ethyl ($)	Incremental QALYs of icosapent ethyl	Incremental cost per QALY ($)
		infarction: 0.808 (SE 0.018) • Post-acute coronary revascularization multiplier of 0.808 (SE 0.038)	infarction: 0.880 (SE 0.018) • Post-acute coronary revascularization multiplier of 1.0 (SE 0)			
1 to 3	CADTH base case			49,392	0.47	105,053

QALY = quality-adjusted life-year; SE = standard error.

Additional scenario analyses were undertaken to consider alternative scenarios from those in the CADTH base case:

- 20-year time horizon: While the latest CADTH economic evaluation guidelines indicate that a lifetime time horizon is most appropriate, a 20-year time horizon was previously used in other CDR pharmacoeconomic submissions for similar indications. Hence, a scenario analysis applying a 20-year time horizon was considered for comparison purposes.

- Alternative post-revascularization utility value: In the CADTH base case, it was assumed that patients would return to their baseline utility values following a revascularization procedure. To determine the impact of this assumption on the CADTH base case, an alternative post-revascularization utility value was identified from a systematic review.[20] Specifically, this systematic review identified literature from a study of patients at multiple time points following percutaneous coronary interventions.[19] The difference between the two time periods (0.868 – 0.776 = 0.092) was applied as the sponsor's post-revascularization utility value.

Full results of CADTH scenario analyses are presented in Table 15. In the 20-year time horizon scenario, incremental costs decreased to $43,522 from $49,392, as reported in CADTH's base case, while QALYs decreased, resulting in an ICUR of $141,118 per QALY gained. The reduction in costs was primarily due to lower icosapent ethyl acquisition costs, while reduction in QALYs was due to a shorter horizon, over which clinical gain continued. The scenario applying an alternative post-revascularization utility value indicated that the model is sensitive to this parameter and that the estimate of icosapent ethyl's cost-effectiveness varies depending on the utility input used. This scenario analysis resulted in an increase in the incremental QALYs and a consequent decrease in the ICUR to $93,657 per QALY gained.

CADTH undertook price-reduction analyses, shown in Table 4. In the CADTH base case, icosapent ethyl would be the optimal therapy at a willingness-to-pay threshold of $50,000 per QALY gained at a price reduction of 43%.

Table 4: CADTH Reanalysis Price-Reduction Scenarios

ICURs of submitted drug versus comparator (cost/QALY)		
Price	**Base-case analysis submitted by sponsor**	**Reanalysis by CDR**
Submitted	$42,797	$105,053
10% reduction	$37,287	$91,961
20% reduction	$31,374	$79,996
30% reduction	$25,797	$67,564
40% reduction	$20,198	$55,646
50% reduction	$14,381	**$42,262**
60% reduction	$8,627	$30,065

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Issues for Consideration

- The clinical experts consulted by CADTH for this review indicated icosapent ethyl may be the sixth or seventh drug added to existing treatment regimens for patients with the indication. Such a large number of drugs may compromise adherence to treatment. Clinicians will have to balance the risk of compromised adherence due to increased pill burden with the potential added benefit of icosapent ethyl.

Patient Input

No patient input was received for this review.

Conclusions

In statin-treated adult patients with elevated triglycerides and other risk factors or at high risk of CVD, the CADTH base-case reanalysis estimated that icosapent ethyl plus statin therapy resulted in increased costs and greater QALYs than statin therapy alone, resulting in an ICUR of $105,053 per QALY gained. 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 compared to relevant comparators currently used in clinical practice, in addition to statin therapy, or in a broader clinical population beyond what has been studied in the REDUCE-IT trial, is unknown. Cost-effectiveness may further differ among patients classified by different risk strata (i.e., primary prevention or secondary prevention) within the indication.

Appendix 1: Cost Comparison

The comparators presented in Table 5 have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice, rather than actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are the sponsor's list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table; as a result, the table may not represent the actual costs to public drug plans.

Table 5: CDR Cost Comparison Table for Treatments Indicated for the Treatment of Hypertriglyceridemia

Drug/ comparator	Strength	Dosage form	Price ($)	Recommended dosage	Average daily drug cost ($)	Average annual drug cost ($)
Submitted drug						
Icosapent ethyl (Vascepa)	1 g	Capsule	2.4500[a]	2 g twice daily	9.80	3,577
Cholesterol absorption inhibitor						
Ezetimibe (Ezetrol)	10 mg	Tablet	0.1811	10 mg daily	0.18	66
Fibrates						
Bezafibrate (Bezalip and generics)	400 mg	Tablet	1.7460	400 mg every morning or at bedtime	1.75	637
Fenofibrate (Lipidil and generics)	100 mg	Capsule	0.6105	3-4 caps divided three times daily before meals	1.83 to 2.4	669 to 891
Fenofibrate (Lipidil Micro and generics)	67 mg 200 mg	Capsule	0.5479 0.2723	67 to 200 mg daily	0.27 to 0.58	99 to 200
Fenofibrate (Lipidil EZ)	48 mg 145 mg	Tablet	0.3560 0.5489	48 to 145 mg daily	0.36 to 0.55	130 to 200
Gemfibrozil (Lopid and generics)	300 mg	Capsule	0.1340	600 mg twice daily after food	0.27	49
Micro-coated fenofibrate (Lipidil Supra and generics)	160 mg	Tablet	0.3116	160 mg daily	0.31	114
Niacin products						
Niacin extended-release (Niaspan FCT)	500 mg 1,000 mg	Tablet	1.3600 1.4400	1,000 to 2,000 mg daily	1.44 to 2.88	523 to 1,051

[a] Sponsor-submitted price.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed July 2019) unless otherwise indicated and do not include dispensing fees. Clinical expert feedback indicated fish oil products containing EPA, with or without DHA, may also be used in practice. Such products are not listed on formularies in Canada and are available over the counter.

Table 6: CDR Cost-Comparison Table for Statins

Drug/ comparator	Strength	Dosage form	Price ($)	Recommended dosage	Average daily drug cost ($)	Average annual drug cost ($)
HMG-CoA reductase inhibitors (statins)						
Atorvastatin (Lipitor and generics)	10 mg 20 mg 40 mg 80 mg	Tablet	0.1734 0.2179 0.2342 0.2342	10 mg to 80 mg at bedtime	0.17 to 0.23	63 to 85
Fluvastatin sodium (Lescol and generics)	20 mg 40 mg	Capsule	0.2202 0.3092	20 mg to 40 mg at bedtime	0.22 to 0.31	80 to 113
Fluvastatin sodium (Lescol XL)	80 mg	Tablet	1.6225	80 mg daily	1.62	592
Lovastatin (Mevacor and generics)	20 mg 40 mg	Tablet	0.4919 0.8985	20 mg to 80 mg at bedtime	0.49 to 1.80	180 to 656
Pravastatin sodium (Pravachol and generics)	10 mg 20 mg 40 mg	Tablet	0.2916 0.3440 0.4143	10 mg to 40 mg at bedtime	0.29 to 0.41	106 to 151
Rosuvastatin calcium (Crestor and generics)	5 mg 10 mg 20 mg 40 mg	Tablet	0.1284 0.1354 0.1692 0.1990	10 mg to 40 mg daily	0.14 to 0.20	49 to 73
Simvastatin (Zocor and generics)	5 mg 10 mg 20 mg 40 mg 80 mg	Tablet	0.1023 0.2023 0.2501 0.2501 0.2501	10 mg to 80 mg at bedtime	0.20 to 0.25	74 to 91

HMG = beta-hydroxy beta-methylglutaryl.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed July 2019) unless otherwise indicated and do not include dispensing fees.

Appendix 2: Summary of Key Outcomes

Table 7: When Considering Only Costs, Outcomes and Quality of Life, How Attractive Is Icosapent Ethyl Plus Statin Therapy Relative to Statins Alone?

Icosapent ethyl plus statin therapy versus statin therapy alone	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	Sponsor's ICUR: $42,797 CADTH revised ICUR: $105,053 per QALY					

CE = cost-effectiveness; ICUR = incremental cost-utility ratio; NA = not applicable; QALY = quality-adjusted life-year.

Appendix 3: Additional Information

Table 8: Submission Quality

	Yes/ good	Somewhat/ average	No/ poor
Are the methods and analysis clear and transparent?	X		
Comments Reviewer to provide comments if checking "no"	None		
Was the material included (content) sufficient?	X		
Comments Reviewer to provide comments if checking "poor"	None		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking "poor"	None		

Table 9: Author Information

Authors of the pharmacoeconomic evaluation submitted to CDR

☐ Adaptation of global model/Canadian model done by the sponsor
☒ Adaptation of global model/Canadian model done by a private consultant contracted by the sponsor
☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the sponsor
☐ 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

Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

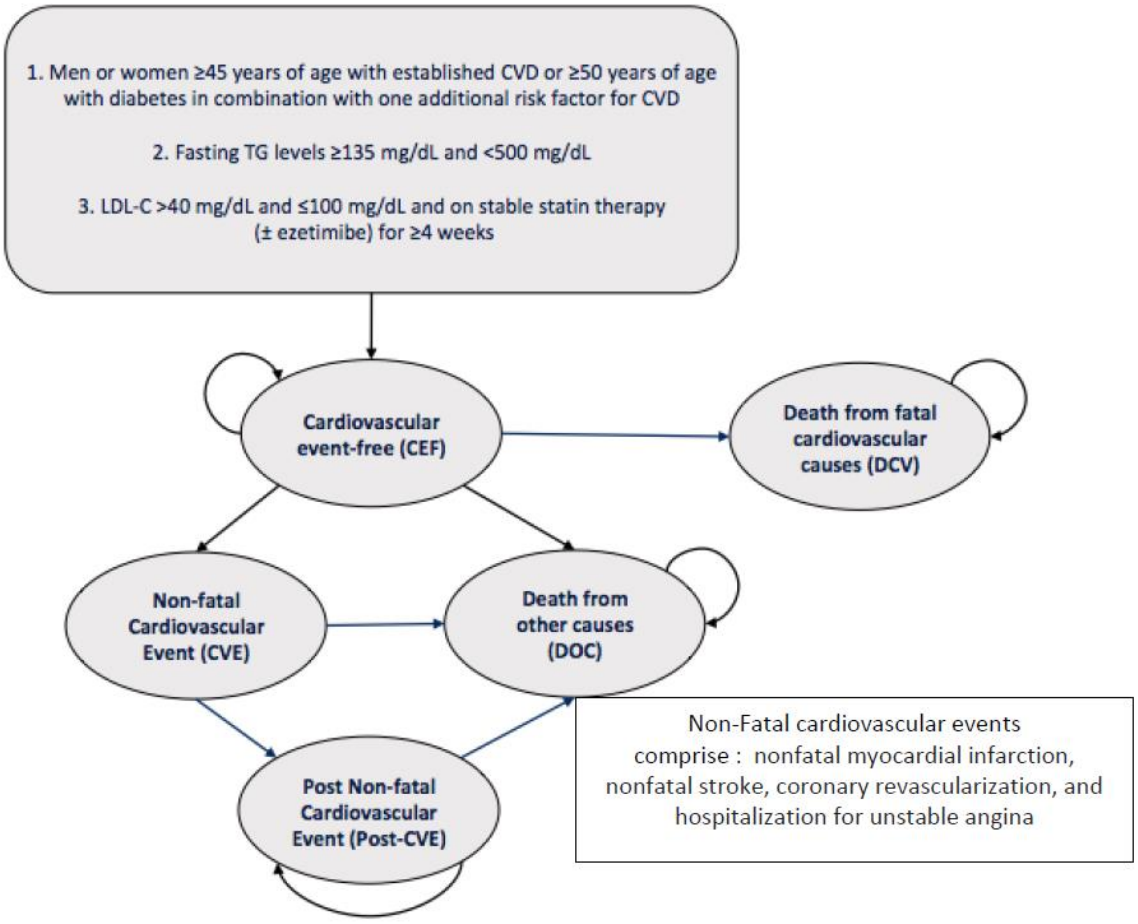
No other health technology assessment agencies have reviewed icosapent ethyl for the requested CADTH Common Drug Review indication.

Appendix 5: Reviewer Worksheets

Sponsor's Model Structure

The sponsor's submitted model consisted of a Markov state-transition model with five states. Patients entered the model as CVE-free (Figure 1). After the first cycle (one year in length), patients could experience death from a fatal CVE, a non-fatal CVE, or death from other causes, or could remain CVE-free. Upon entering the non-fatal CVE state, patients could either experience death from other causes or enter a post–non-fatal CVE state in the next model cycle. Patients in the post–non-fatal CVE state would remain in this health state until their death and would be at higher risk of subsequent CVEs.[3]

Figure 1: Model Schematic — Cohort-Level Markov State-Transition Model



CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride.
Source: Sponsor's pharmacoeconomic submission.[3]

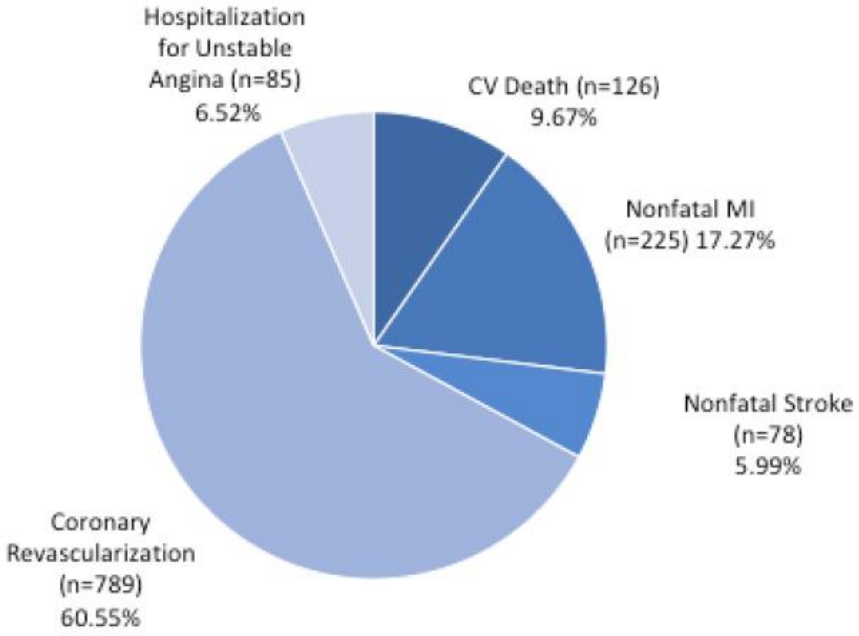
Table 10: Data Sources

Data input	Description of data source	Comment*
Baseline characteristics	REDUCE-IT trial[4]	The baseline distribution of statin therapy is not representative of guidance from clinical practice guidelines. The clinical experts consulted by CADTH for this review indicated that 60% of patients would be on high-intensity statin therapy, as per current clinical practice guidelines, in addition to icosapent ethyl. In the sponsor's submission, it was assumed that the intensity of statin therapy would be in line with the baseline characteristics from the REDUCE-IT trial (6.4% low intensity, 62.7% moderate intensity; 30.9% high intensity), which does not align with the clinical experts' feedback. The distribution of baseline statin intensity was balanced between treatment groups in REDUCE-IT and was unlikely to influence the results.
Efficacy and AEs	REDUCE-IT trial[4] Relative treatment effects for primary cardiovascular events (defined as non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, and hospitalization for unstable angina) in the form of hazard ratios were applied to parametric curves for the statin-only arm of the REDUCE-IT[4] trial in the first five years for each of the individual cardiovascular events included in the model. For subsequent events, event rates from each treatment arm of the REDUCE-IT[4] trial were used to populate the transition probabilities for the respective comparators for the first five years of the model time horizon. Beyond the five-year time horizon, no treatment effects were applied. In other words, the survival curves were assumed to be parallel thereafter.	Proportional hazards were assumed and were appropriate, based on diagnostic test results provided by the sponsor. A plot of log of negative log of estimated survivor functions was provided; it tested whether including a time-dependent covariate of treatment by survival time interaction term in the Cox proportional hazards model was statistically significant. Only AEs that were statistically significantly different were considered. Although this is a conservative approach, CADTH economic guidelines recommend incorporating AEs that are most clinically meaningful. Excluded AEs are unlikely to have significantly affected model results, although this remains uncertain. Not appropriate; see "Limitations of the Sponsor's Submission" in the main report
Natural history	Based on the best-fitting parametric curve of individual patient-level data from the statins-only arm of the REDUCE-IT trial for the primary end points;[3,4] data up to five years were available	Likely appropriate; see concerns raised under baseline characteristic

Data input	Description of data source	Comment*
Utilities	Health state utilities and AE disutilities were identified from the literature.[12-15,21] Health state utilities were derived by combining the utility values of the component health states multiplicatively with the baseline utility value; AE utilities were incorporated via an additive approach.	Errors were noted, as utility values used in the sponsor's model differed from the utility values reported in the literature; see "Limitations of the Sponsor's Submission" in the main report
Mortality	Risk of mortality from cardiovascular causes was derived from the REDUCE-IT trial.[4] Baseline mortality from Statistics Canada Life Tables;[9] mortality rate in years following non-fatal cardiovascular event were adjusted based on relative risk of death due to prior cardiovascular event, as reported in literature[10,11]	Appropriate The manufacturer included cardiovascular mortality as an event in the model, in addition to mortality from all causes, which was obtained from Statistics Canada life tables.[9] The value for mortality from all causes was obtained from Statistics Canada and would include mortality from cardiovascular events. As the values used in the model were not adjusted to account for the separate CVD mortality that was already included in the model, mortality was overestimated. The impact of this limitation on model results is likely minor.
Resource use and costs		
Drug	Cost of icosapent ethyl was obtained from the sponsor. Cost of background medications was obtained from the Ontario Drug Benefit (ODB) e-formulary.[16]	Appropriate
Administration	Follow-up and monitoring costs for treatment were included in the model. Resource use for follow-up and monitoring was based on a combination of guidelines and clinical expert opinion, with costs obtained from the Ontario Schedule of Benefits.[8,22] 80% of patient management was assumed to be conducted in a general practitioner setting.	Likely appropriate; unlikely to impact model results
Event	Costs related to cardiovascular events were obtained from a combination of the Ontario Case Costing Initiative[17] and published literature.[23-25]	Appropriate
AEs	AE costs were obtained from the Ontario Case Costing Initiative.[23]	Appropriate

AE = adverse event; CVD = cardiovascular disease.

Figure 2: Distribution of Secondary Cardiovascular Events



CV = cardiovascular; MI = myocardial infarction.
Source: Sponsor's pharmacoeconomic submission.[3]

Table 11: Sponsor's Key Assumptions

Assumption	Comment
The distribution of statin therapy intensities was assumed to match the distribution of intensities of statin therapies in the REDUCE-IT trial.	Not appropriate; the clinical experts consulted by CADTH for this review indicated 60% of patients would be on high-intensity statin therapy as per current clinical practice guidelines. This does not match the distribution of patients in the REDUCE-IT trial. The impact on results is unknown.
A 20-year time horizon was appropriate to capture all differences in costs and QALYs.	Not appropriate; see "Limitations of the Sponsor's Submission" in the main report.
The median follow-up of REDUCE-IT was five years; therefore, during the initial five year period of the model, estimates of risk and benefits for icosapent ethyl versus placebo for first and subsequent events reflected the REDUCE-IT trial results. After the initial five year period, event rates for icosapent ethyl were assumed to equal that for the placebo group.	Although the assumption could be appropriate if patients are expected to discontinue treatment after five years, feedback from clinical experts indicated that patients were likely to remain on treatment beyond the trial duration and to continue to benefit from treatment beyond a five-year time period.
The proportion of cardiovascular events occurring was assumed to be constant over time.	Appropriate; the proportional hazards assumption holds for all cardiovascular events included in the model.
Treatment cost beyond the five year period included only costs for statin therapy (no costs for icosapent ethyl).	Removal of icosapent ethyl costs beyond the first five years was inappropriate, given feedback from clinical experts indicating patients would remain on icosapent ethyl beyond the trial duration.

QALY = quality-adjusted life-year.

Sponsor's Results

The results of the sponsor's base case are presented in Table 2. The disaggregated costs from the sponsor's base case are presented in Table 2.

Table 12: Expected Discounted QALYs and Costs by Treatment and Cost Categories, Sponsor's Base Case

	Costs ($)					QALYs	
	Drug cost	Cardiovascular disease cost – first event	Cardiovascular disease cost – subsequent event	Follow-up	Adverse events	Health states	Treatment-related adverse events
Statin therapy alone (a)	2,043	36,448	1,388	1,760	701	9.59	–0.004
Icosapent ethyl plus statin therapy (b)	18,807	32,372	766	1,960	958	9.88	–0.005
Difference (b – a)	16,764	–4,075	–622	200	257	0.29	–0.001

QALY = quality-adjusted life-year.

Source: Sponsor's submission.[3]

The expected number of events for each comparator per 1,000 patients is presented in Table 13.

Table 13: Expected Events per 1,000 Patients

Disaggregated costs	Icosapent ethyl plus statin	Statin only
Total first events		
CV death	90	100
Non-fatal MI	180	190
Non-fatal stroke	60	70
Coronary revascularization	140	150
Hospitalization for unstable angina	70	80
Total subsequent events		
Death associated with post-CVE	10	20
Non-fatal MI	20	40
Non-fatal stroke	10	10
Coronary revascularization	70	120
Hospitalization for unstable angina	10	10
Difference (icosapent ethyl plus statins versus statins only)		
CV death	–9.13	
Non-fatal MI	–15.08	
Non-fatal stroke	–5.22	
Coronary revascularization	–11.77	
Hospitalization for unstable angina	–6.07	
Primary end point	–47.26	
Subsequent non-fatal events	–92.65	
Total events	–139.91	

Source: Sponsor's submission.[3]

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Table 14: Summary of Results of the CADTH Base Case

		Total costs ($)	Incremental cost of icosapent ethyl ($)	Total QALYs	Incremental QALYs of icosapent ethyl	Incremental cost per QALY ($)
Manufacturer's base case	Statin therapy alone	42,341		9.58		
	Icosapent ethyl plus statin therapy	54,864	12,523	9.88	0.29	42,797
Lifetime time horizon	Statin therapy alone	67,423		10.96		
	Icosapent ethyl plus statin therapy	79,420	11,997	11.32	0.36	32,902
Icosapent ethyl efficacy and costs applied for whole time horizon	Statin therapy alone	41,817		9.67		
	Icosapent ethyl plus statin therapy	85,281	43,464	10.09	0.42	104,098
Corrected utility values for cardiovascular events	Statin therapy alone	41,933		10.13		
	Icosapent ethyl plus statin therapy	54,508	12,575	10.35	0.23	55,641
CADTH base case	Statin therapy alone	67,713		11.56		
	Icosapent ethyl plus statin therapy	117,105	49,392	12.03	0.47	105,053

QALY = quality-adjusted life-year.

Table 15: Summary of Results of the CADTH Scenario Analyses

		Total costs ($)	Incremental cost of icosapent ethyl ($)	Total QALYs	Incremental QALYs of icosapent ethyl	Incremental cost per QALY ($)
20-year time horizon	Statin therapy alone	41,921		10.13		
	Icosapent ethyl plus statin therapy	85,443	43,522	10.43	0.31	141,118
Alternative post-revascularization utility value	Statin therapy alone	67,759		11.34		
	Icosapent ethyl plus statin therapy	117,022	49,263	11.86	0.53	93,657

QALY = quality-adjusted life-year.

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