CADTH

CADTH Drug Reimbursement Review

Pharmacoeconomic Report

RANOLAZINE (CORZYNA)

(KYE Pharmaceuticals)

Indication: Stable angina pectoris, adults

Service Line: CADTH Common Drug Review
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CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

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Abbreviations

BIA	budget impact analysis
CCS	Canadian Cardiovascular Society
EQ-5D	EuroQol 5-Dimensions
ICER	incremental cost-effectiveness ratio
QALY	quality-adjusted life-year
SAQ	Seattle Angina Questionnaire
SAQAF	Seattle Angina Questionnaire – Angina Frequency

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Ranolazine (Corzyna), 500 mg and 1,000 mg extended-release oral tablets
Submitted price	Ranolazine 500 mg, 1,000 mg: $3.50 per tablet
Indication	Proposed: In adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta-blockers and/or calcium antagonists)
Health Canada approval status	Under review (pre-NOC)
Health Canada review pathway	Priority review
NOC date	Anticipated: January 2, 2021
Reimbursement request	As per indication
Sponsor	KYE Pharmaceuticals Inc.
Submission history	Previously reviewed: No

NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis
Target population	Adults 18 years and older diagnosed with stable angina who require therapy beyond first-line treatment
Treatment	Ranolazine, as an add-on to standard therapy
Comparator	Standard therapy[a]
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, costs
Time horizon	1 year
Key data source	ERICA trial
Submitted results for base case	ICER = $24,477 per QALY (incremental costs: $1,860; incremental QALYs: 0.08)
Key limitations	• There was considerable uncertainty in the underlying clinical evidence: the strength of comparative effectiveness, the effect on health-related quality of life, and the representativeness of the pivotal trial populations to a Canadian patient population. These limitations impact several key health economic assumptions in ways that could not be addressed. • The sponsor's pharmacoeconomic model does not adequately reflect the clinical management of angina patients. Treatment effectiveness is modelled in terms of a reduction in the frequency of angina symptoms. In practice, treatment decisions may be made based on reductions in symptom severity both in addition to and irrespective of the frequency of episodes. The sponsor's model does not consider symptom severity, limiting its ability to reflect the anticipated use of ranolazine. • The estimated rate of response (i.e., the proportion of patients who have a reduced frequency of episodes) to ranolazine was overestimated in the cost-effectiveness model and did not reflect response to ranolazine in the ERICA trial. • The sponsor's estimates of treatment costs were not consistent with CADTH guidelines, overestimating the cost of treatment. • The health-state utility values for the model health states are uncertain due to the mapping approach used. • Treatment discontinuation was permitted only during the first month of treatment, which is not consistent with data observed from long-term studies.
CADTH reanalysis results	• In the CADTH reanalysis, the rate of ranolazine response was reduced, alternative health-state costs were adopted, a wider range of possible utility values was considered, and the analysis horizon was extended to a lifetime horizon. CADTH was unable to consider the impact of angina severity. • Due to methodologic limitations with the sponsor's submitted model, the cost-effectiveness of ranolazine remains highly uncertain within this indication.

ICER = incremental cost-effectiveness ratio; QALY= quality-adjusted life-year.

[a] Assumed to be beta-blockers and/or calcium-channel agonists and/or long-acting nitrates. Ranolazine was modelled as an add-on therapy (i.e., in addition to standard therapy). Accordingly, the sponsor assumed that the incremental cost attributable to standard therapy was $0 in its base case.

Conclusions

CADTH undertook reanalyses to address limitations in the sponsor's submission, including using an appropriate value for the rate of ranolazine response, correcting health-state resource costs, adopting a wider range of possible utility values, and extending the analysis to a lifetime horizon.

CADTH was unable to address several important limitations associated with the model structure. Notably, the sponsor's model considered only the frequency of angina symptoms and did not consider symptom severity, a clinically relevant marker of treatment response. It is unclear whether the small incremental quality-adjusted life-year (QALY) gains would provide meaningful benefit to patients. Given these limitations, the uncertainty regarding the strength of the comparative effectiveness evidence, and the generalizability of the pivotal trial evidence to a Canadian population, the comparative clinical effectiveness of ranolazine is highly uncertain. The cost-effectiveness of ranolazine is therefore also uncertain.

Stakeholder Input Relevant to the Economic Review

No patient input was received for this submission.

Economic Review

The current review is for ranolazine (Corzyna) for adults aged 18 years and older diagnosed with stable angina pectoris and who require therapy beyond first-line treatment.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

Ranolazine is indicated as an add-on to therapy for the symptomatic treatment of stable angina pectoris (hereafter referred to as stable angina) in patients who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta-blockers and/or calcium antagonists).[1] The sponsor submitted a cost-utility analysis of ranolazine as an add-on to standard therapy for adults with stable angina who require therapy beyond first-line treatment. Standard therapy was assumed to be beta-blockers and/or calcium-channel agonists and/or long-acting nitrates.[2] The modelled patient population had baseline characteristics similar to those of participants in the ERICA trial, a 7-week multi-centre, placebo-controlled randomized clinical trial involving 565 adult patients with stable coronary artery disease and at least 3 anginal attacks per week despite taking amlodipine (10 mg per day).[3]

Two strengths of ranolazine are available (500 mg and 1,000 mg) at a unit cost of $3.50 per tablet, for an annual cost of $2,555. The recommended dosage is 500 mg twice daily, which may be increased to 1,000 mg twice daily as needed on the basis of clinical symptoms.[4] No cost was associated with standard therapy in the model, as this was assumed to apply equally to both groups.

The sponsor adopted a 1-year horizon, with the analysis conducted from the perspective of the publicly funded health care payer. Costs and clinical outcomes were not discounted in the base-case analysis. The model cycle length was 1 month.

Model Structure

The economic analysis was conducted using a 5-state Markov model, with health states related to the frequency of angina symptoms (monthly angina, weekly angina, daily angina, and no angina) or death (Appendix 3). The frequency of angina symptoms was defined on the basis of Seattle Angina Questionnaire – Angina Frequency (SAQAF) scores. The "no angina" state was defined as a score of 100 points on the SAQAF, while scores of 61 to 99, 31 to 60, and 0 to 30 represented the monthly angina, weekly angina, and daily angina health states, respectively. At cohort entry, patients were distributed between the monthly angina (6.1%), weekly angina (71.0%), and daily angina (22.9%) states; no patients started in the no angina state. Patients could transition between health states only during the first cycle (i.e., first month after the start of ranolazine treatment). In subsequent cycles, patients

were assumed to stay in the same health state for the remainder of the model's time horizon or until death (i.e., no further improvements or losses could occur beyond the first cycle). Movement between states in the first cycle was based on treatment-specific probabilities derived from the ERICA trial, as published in a previous economic evaluation.[5] Those who had no clinical response (i.e., did not improve by at least 1 health state) in the first cycle or who experienced an adverse event were assumed to discontinue ranolazine and to continue on standard therapy alone. Discontinuation could occur only during the first cycle, and only patients taking ranolazine could discontinue treatment.

Model Inputs

The baseline patient characteristics in the model were aligned with those of the ERICA trial[3] patient population. Participants in ERICA were randomized to receive ranolazine (500 mg twice daily for the first week followed by 1,000 mg twice thereafter). At baseline, the mean number of angina episodes per week was 5.63, and 43% to 46% of participants had concomitant use of long-acting nitrates. The mean age of participants in ERICA was 61 to 62 years, with 27% to 28% female participants. Previous coronary interventions were uncommon among participants in ERICA, with 10% to 12% having previous coronary artery bypass grafting and 9% to 12% having previous percutaneous coronary intervention. The distribution of patients between model health states at cohort entry was based on the distribution at baseline in the ERICA trial.

Transition probabilities in the economic model were obtained from a 2015 economic evaluation of ranolazine by Coleman and colleagues,[5] which reported having calculated the transition probabilities based on individual patient data from ERICA. The clinical efficacy of ranolazine, as well as the standard therapy, in terms of transition between health states, was based on the ERICA trial.[3] The transition probabilities for ranolazine were based on participants randomized to ranolazine who had a clinical response during the treatment period (i.e., improved by at least 1 health state). For standard therapy, the transition probabilities were based on all participants randomized to placebo regardless of clinical response.

In the model, use of sublingual nitroglycerin was included as a rescue medication. The rate of use of nitroglycerin was based on the ERICA trial and was assumed to differ between patients receiving ranolazine (0.39 units per day) and standard therapy (0.51 units per day).[3]

Mortality among patients with stable angina was assumed to be equivalent to age- and gender-standardized mortality rates in Canada, the source of which was not referenced by the sponsor. No adverse events were explicitly included in the sponsor's economic evaluation, although patients could discontinue ranolazine in the first month of treatment in the event of an adverse event or lack of effectiveness. The probability of treatment discontinuation in the first month (1.1%) was adopted from the Coleman study.[5] Patients who discontinued ranolazine treatment were assumed to have costs and outcomes similar to those of patients receiving standard therapy following discontinuation.

Health-state utility values associated with each health state were obtained from the Coleman study,[5] which mapped SAQAF scores to the EuroQol 5-Dimensions (EQ-5D) questionnaire on the basis of observed data in the ERICA trial by use of a mapping algorithm.[6] Treatment costs included ranolazine and sublingual nitroglycerin rescue therapy; no cost was associated with standard therapy in the model. The price of ranolazine was provided by the sponsor,[1] and the price of sublingual nitroglycerin was obtained from the Ontario Drug Benefit Formulary,[7] with an 8% mark-up fee and an $8.00 dispensing fee applied to each

drug. The cost of treating stable angina was obtained from a 2003 to 2005 study involving 117 patients with stable angina in Toronto, Ontario,[8] inflated to 2020 dollars.[9] This estimate was assumed to reflect the cost of treating daily angina (i.e., the daily angina health state), and the sponsor applied a ratio to estimate the costs associated with the weekly angina, monthly angina, and no angina health states (e.g., the costs associated with weekly angina were assumed to be 65% of the costs of daily angina).

Summary of Sponsor's Economic Evaluation Results

The sponsor submitted cost-effectiveness estimates based on both deterministic and probabilistic (1,000 iterations for the base case) analyses. The findings of the probabilistic and deterministic analyses were similar; however, only the probabilistic results are presented below.

Additional details pertaining to the sponsor's submission are available in Appendix 3.

Base-Case Results

In the sponsor's base-case analysis, the addition of ranolazine to standard therapy was associated with incremental costs of $1,860 compared with standard therapy alone over the 1-year analysis period. The addition of ranolazine was associated with a gain of 0.08 QALYs over the same period, resulting in an incremental cost-effectiveness ratio (ICER) of $24,477 per QALY gained.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug[a]	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. standard therapy (per QALY)
Standard therapy	4,960	—	0.68	—	—
Ranolazine plus standard therapy	6,820	1,860	0.75	0.08	24,477

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

[a] Standard therapy was assumed to apply equally to both groups, and the costs of standard therapy was set to $0 in both groups (i.e., incremental cost of standard therapy was zero).

Source: Sponsor's pharmacoeconomic submission.[2]

Sensitivity and Scenario Analysis Results

The sponsor conducted several sensitivity and scenario analyses. These included varying the time horizon (6 months, 5 years), the discount rate (0%, 3%), assuming no ranolazine discontinuation, removing costs related to sublingual nitroglycerin use, and taking a societal perspective (i.e., including productivity costs). In all scenarios, adding ranolazine to standard therapy was a more cost-effective option than standard therapy alone at a $50,000 willingness-to-pay threshold.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **Strength of the available clinical evidence**. The CADTH clinical review identified issues within the evidence submitted by the sponsor that have meaningful implications for the interpretation of the economic evidence. First, the comparative effectiveness of ranolazine may not be clinically important to patients. The sponsor's model is driven by the same comparative effectiveness data, which raises questions about its ability to reflect patient experience. Second, the impact of ranolazine on health-related quality of life has not be demonstrated. The sponsor assigned health-state utility values (which are related to quality of life) to the model health states, but the validity of this approach is questionable. Further, while the values selected (Table 11) suggest a high degree of certainty for these parameters, this was not supported by the clinical evidence. Third, the clinical review raised questions about the generalizability of the pivotal trial evidence to the Canadian population with stable angina. The cumulative effect of these concerns indicates that all parameters in the model have a higher level of uncertainty than is reflected in the statistical error around each parameter estimate. This renders significant uncertainty in the economics, where the predicted benefit of ranolazine (in terms of QALYs gained) may not be realized.
    - CADTH was not able to directly address these concerns with the underlying clinical evidence. Standard approaches for investigating the impact of uncertainty — scenario analyses, sensitivity analyses, probabilistic analyses — were undertaken but are not sufficient to correct unknown and unquantifiable uncertainty within key parameters and assumptions about comparative efficacy.
- **The model structure does not adequately reflect the management of angina in clinical practice.** The health states in the sponsor's model were based on the frequency of angina symptoms (daily, weekly, monthly, no symptoms), with treatment response defined as improvement by at least 1 state (e.g., moving from weekly to monthly symptoms). The clinical experts consulted by CADTH indicated that the goal of angina treatment is subjective and depends on individual patients' values and preferences, and response to therapy may include a reduced frequency of angina symptoms, improved quality of life, or improved functionality. The clinical experts noted that a reduction in angina severity, graded on the basis of the Canadian Cardiovascular Society (CCS) classification system,[10] is generally clinically meaningful. For example, class IV symptoms (i.e., those that prevent a patient from carrying out any physical activity without discomfort) are the most burdensome, and reducing these to class III (i.e., marked limitation of ordinary physical activity) would generally be an important change for patients. Exercise tolerance was also identified as an important outcome to some patients.

  As noted in the CADTH clinical review, in the ERICA trial, use of ranolazine was associated with an improvement in angina frequency (assessed by use of the SAQAF), although the difference between ranolazine and placebo may not be clinically important. There was no statistically significant difference for any other SAQ domain (physical limitation, anginal stability, disease perception, treatment satisfaction).
    - The sponsor's model does not incorporate clinically important aspects of angina treatment such as symptom severity. CADTH was unable to address this limitation.
- **The clinical response to ranolazine was overestimated by the sponsor.** The sponsor assumed that all patients who receive ranolazine will achieve a clinical response (defined as improving by at least 1 health state; e.g., moving from weekly to monthly angina episodes). Alternatively, the response rate for standard therapy was based on the results from all participants receiving standard therapy in the ERICA trial. The assumption that 100% of patients receiving ranolazine will experience a clinical response is not consistent with the experience of the clinicians consulted by CADTH or the findings from the ERICA

trial (52% of participants who received ranolazine had a clinical response compared with 42% in the placebo arm).[5] This assumption biased the sponsor's analysis in favour of ranolazine.

It should also be noted that this assumption was not stated explicitly and was in conflict with the sponsor's description of the model's structure and function. Instead, this was only determined based on CADTH's review of the sponsor's model.

- CADTH asked the sponsor to provide transition probabilities reflective of all patients who received ranolazine in the ERICA trial; these were not provided. In the CADTH reanalyses, a 52% probability of clinical effectiveness of ranolazine was adopted, consistent with the Coleman et al. (2015)[5] analysis of individual patient data from the ERICA trial. However, CADTH was unable to scale the response adjustment by angina severity due to the lack of data.

- **Health-state costs were estimated inappropriately.** The sponsor incorporated costs as reported by McGillion et al.,[8] who reported "direct," "system," and "indirect costs." In this study, direct costs were those incurred by patients ("all out-of-pocket costs related to the care and management of angina, or to angina-related disabilities that were incurred by participants, including money paid to health care professionals who came to their homes; to attend health care appointments outside their homes; to have household work done in the home; for angina-related medications; and for supplies or equipment related to heart disease"),[8] while systems costs included those paid by the Ontario Health Insurance Program and private insurers. The inclusion of costs paid by patients and private insurers is inappropriate given the perspective of the analysis. Angina-related medications were also included in the health-state costs, which potentially double-counts the cost of standard therapy.

  Additionally, the sponsor applied the costs reported by McGillion et al.[8] to the daily angina health state. To estimate the costs associated with the remaining health states (weekly angina, monthly angina, no angina), the sponsor applied the ratio of costs between the daily and other health states as reported from the MERLIN-TIMI36 trial.[11] CADTH determined that the costs used for these ratios were inappropriate, as they included medication costs.

  - To address the inappropriate cost sourcing, CADTH replaced costs from the McGillion study[8] with those from a population-based retrospective cohort of 20,956 adult patients with CCS class 0 to IV stable angina in Ontario between 2008 and 2013.[12] These costs were assumed to reflect the cost of managing daily angina. The revised ratio of costs (i.e., with medication costs removed) from the MERLIN-TIMI36 trial was applied to derive the costs associated with the remaining health states. The cumulative effect of correcting for these issues favoured the cost-effectiveness of ranolazine.

- **The utility values associated with the model health states are uncertain.** The sponsor adopted health-state utility values from a previous economic evaluation of ranolazine (Table 11).[5] Coleman et al.[5] mapped individual patient SAQ scores from the ERICA trial to the EQ-5D questionnaire.[6] Others[13] have used the same equation to map SAQ scores from the ERICA trial to the EQ-5D, reporting similar point estimates for each health state but wider ranges of possible utility values for each state. Even within these wider ranges, the utility values between model states do not overlap. This assumption may not be plausible given that symptom severity may vary independently from frequency (e.g., a person may find it equally preferable to have frequent mild episodes or to have episodes that are infrequent but severe).

  CADTH notes that the mapping equation used by the sponsor[6] includes 3 of 5 SAQ domains (angina frequency, physical limitation, and disease perception) as well as demographic variables (age, sex, percutaneous coronary intervention, and coronary artery bypass grafting). However, alternative equations[14] have included all 5 domains of the SAQ but no demographic variables. These approaches result in different utility values for each model health state.[13]

- To account for the uncertainty in the utility values for the model health states, CADTH took a conservative approach and adopted the range of possible utility values from the Kohn analysis in the base case.[13] The impact of this was explored in scenario analyses. CADTH further explored the uncertainty associated with the utility estimates by adopting alternative utility estimates in its scenario analysis.

- **Ranolazine discontinuation may be modelled inappropriately.** The sponsor assumed that "only patients assigned to receive ranolazine at the initiation of the model could discontinue therapy (for lack of efficacy or adverse drug events) and discontinuation could only occur during the first cycle. The probability of discontinuation in the first 4 weeks of therapy was reported as 1.1%," which was adopted from a previous economic evaluation.[5] However, CADTH noted that the original study reported discontinuation owing to adverse events (1.1%) separately from discontinuation owing to non-response.[5] Further, it is unlikely that participants would discontinue ranolazine only during the first month of treatment. While the long-term discontinuation of ranolazine in this population is uncertain, among participants who took ranolazine as part of the CARISA trial, approximately 30% had discontinued ranolazine by the end of the first year (for any reason); this increased to approximately 40% by 2 years.[15]
  - Because of structural assumptions within the model and a lack of evidence about the clinical effect of discontinuing ranolazine, CADTH could not address this limitation.
- **Parameter uncertainty was inappropriately incorporated.** For several model parameters (e.g., health-state costs, discontinuation rate, cohort age), the sponsor arbitrarily incorporated uncertainty as ± 20% of the mean value, which does not reflect the true uncertainty around the model's possible parameter values. Furthermore, a normal distribution was assumed as part of the probabilistic sensitivity analysis calculations, including for parameters that are not normally distributed (e.g., costs).
  - CADTH was unable to address this limitation due to a lack of information about the true uncertainty of these parameters, and structural limitations within the model. As a result, CADTH could not adequately account for uncertainty and cannot estimate the probability of ranolazine being cost-effective at any willingness-to-pay threshold.

The following key assumptions were made by the sponsor and have been appraised by CADTH (Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
The cost-effectiveness of ranolazine was assessed over a 1-year time horizon.	Unreasonable. CADTH economic guidelines state that the time horizon should be long enough to sufficiently capture all potential costs and effects, and that when modelling a chronic condition, a lifetime horizon is most appropriate.[16] The clinical experts consulted by CADTH indicated that, owing to the chronic nature of stable angina, treatment with ranolazine would continue indefinitely for patients who had a favourable response to ranolazine. In the CADTH base case, the time horizon has been extended to 40 years. Changes in angina frequency over time could not be reflected, nor could changes in ranolazine efficacy.

Sponsor's key assumption	CADTH comment
Transition between health states was restricted to the first model cycle, after which time patients were assumed to stay in the same health state or to transition to the death health state.	Reasonable. The sponsor assumed that the majority of the effect of ranolazine is seen in the first few weeks of treatment on the basis of data from the TERISA trial,[17] which evaluated the efficacy of ranolazine (1,000 mg twice daily) on a background of 1 or 2 antianginal therapies in patients with type 2 diabetes mellitus and chronic stable angina. The clinical experts consulted by CADTH indicated that patients may see an effect within the first few days of taking ranolazine. However, the experts noted that, while the effect of ranolazine may be observed quickly within the framework of a clinical trial, in practice it may take longer to determine clinical effectiveness, because an individual patient may be having symptoms infrequently or only with a specific activity. The assumption that patients would remain in the same health state following the first cycle was deemed reasonable by the clinical experts consulted by CADTH, who indicated that the initial effect of ranolazine treatment would likely be maintained as long as they remained on treatment, provided that their underlying coronary artery disease does not progress and that they do not increase their activity level.
The risk of death was consistent across health states.	Uncertain. The risk of death varies with angina frequency, with patients having daily angina at greatest risk.[18,19] While a mortality benefit has not been observed for ranolazine,[18] it may affect the distribution of patients between the health states and indirectly affect the risk of death.
The safety profiles of both treatments were assumed to be equivalent, and adverse events were not included in the model.	Uncertain. The sponsor's model did not incorporate costs or quality-of-life decrements due to adverse events. As noted in the clinical review, the 3 key trials of ranolazine had short treatment durations and the reporting of harms data was incomplete. Adverse events were experienced by 27% to 40% of participants who received ranolazine in the ERICA,[3] CARISA,[15] and TERISA[17] trials, and 1.8% to 5.4% of participants experienced a serious adverse event.
Costs related to monitoring were not included in the sponsor's submission.	Unreasonable. The clinical experts consulted by CADTH indicated that patients taking ranolazine would require periodic ECGs for monitoring, owing to the QT-prolongation effect of ranolazine.[4] The requirement for ECG monitoring at baseline and during ranolazine treatment has been previously noted.[20] Additionally, the clinical experts indicated that digoxin levels should be monitored for patients with concomitant digoxin use; however, this may affect a small proportion of eligible patients.
In the sponsor's base case, the use of sublingual nitroglycerine was assumed to be 0.39 units per day in the ranolazine group and 0.51 units in the standard care group.	Uncertain. The use of sublingual nitroglycerine as a rescue treatment was incorporated into the sponsor's analysis according to the treatment received, not the frequency or severity of angina attack; however, because of the low price of sublingual nitroglycerine (Appendix 1), the impact of this on the ICER is likely negligible.
The submitted pharmacoeconomic analysis assumed that ranolazine would be added to standard therapy and that standard therapy would be applied equally in the presence and absence of ranolazine (i.e., there would be no change in the cost of standard therapy).	Uncertain. Clinical experts consulted by CADTH indicated that, for patients taking ranolazine in addition to standard therapy, the composition and dosage of standard therapy would be determined on an individual patient basis. For patients who had previously experienced an adverse event with standard therapy, the dosage of background treatments may be decreased if ranolazine is added. The sponsor's model did not allow this assumption to be tested, and there was insufficient evidence to estimate the proportion of patients reducing standard therapy. Given the relatively low impact that reduction in standard therapy would have on overall costs, the impact of this assumption on the ICER is likely small.

ECG = electrocardiogram; ICER = incremental cost-effectiveness ratio.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH reanalyses addressed several limitations within the economic model and are summarized in Table 5. CADTH was unable to address the structural limitation of the model as it relates to lack of consideration of patient-important outcomes of treatment (e.g., severity of angina episodes).

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
1. Removal of mark-up and dispensing fees	An 8% mark-up and $8 dispensing fee was applied to each drug.	Mark-up and dispensing fees were removed.
Changes to derive the CADTH base case		
1. Clinical effectiveness of ranolazine	All patients who received ranolazine were assumed to have a clinical response (i.e., improve by at least 1 health state).	A proportion of patients (52%) were assumed to have a clinical response to ranolazine, consistent with the analysis of individual patient data from the ERICA trial by Coleman 2015.[5]
2. Health-state costs	Costs associated with the daily angina health state were based on direct costs reported by McGillion (2008),[8] which inappropriately comprised costs not relevant to the public health care payer (e.g., out-of-pocket costs to patients).	Costs associated with the daily angina health state were based on costs reported by Szpakowski (2017)[12] after the subtraction of medication costs from the total reported costs.
3. Ratio of costs between health states	The ratio of costs between the daily angina health state and the weekly, monthly, and no angina states was based on the ratio of total costs reported in the MERLIN-TIMI36 trial.[11] Total costs reported from MERLIN-TIMI36 included medication costs, which are accounted for separately within the model. (Original ratio: daily angina: 1; weekly angina: 0.65; monthly angina: 0.56; no angina: 0.42.)	CADTH subtracted medication costs from the total costs reported for MERLIN-TIMI36[11] and recalculated the ratio of costs between health states. (Revised ratio: daily angina: 1, weekly angina: 0.58; monthly angina: 0.47; no angina: 0.29.).
4. Range of possible utility values for each health state	The sponsor adopted utility values from a previous economic evaluation of ranolazine.[5] These values were mapped from the SAQ to the EQ-5D, using data from the ERICA trial, by use of the Goldsmith[6] mapping equation. Daily angina: 0.54 (0.52 to 0.56) Weekly angina: 0.65 (0.64 to 0.66) Monthly angina: 0.76 (0.75 to 0.77) No angina: 0.87 (0.84 to 0.90)	Others have similarly analyzed the ERICA SAQ data and have reported a wider range of possible values for each health state (with the same point estimate).[13] CADTH adopted the wider range to account for uncertainty in the utility values. Daily angina: 0.54 (0.52 to 0.61) Weekly angina: 0.65 (0.61 to 0.70) Monthly angina: 0.76 (0.70 to 0.81) No angina: 0.87 (0.77 to 0.91)
5. Extended time horizon	1 year	Lifetime (40 years)
CADTH base case	—	Reanalysis 1, 2, 3, 4, and 5

EQ-5D = EuroQol 5-Dimensions; SAQ = Seattle Angina Questionnaire.

CADTH's base case results are presented in Table 6. Additional reanalyses and the disaggregated results are presented in Appendix 4.

In CADTH's base case, adjunctive ranolazine was associated with higher costs compared with standard therapy alone (incremental: $15,081) and higher QALYs (incremental: 0.342) over a 40-year time horizon (ICER $44,067 per QALY). Owing to methodological limitations within the sponsor's model, CADTH is unable to comment on the impact of parameter uncertainty on the decision uncertainty surrounding the ICER. However, given that the sponsor's definition of treatment response does not consider symptom severity, and the lack of generalizability of the pivotal trial identified with the CADTH clinical review, it is reasonable to conclude that the level of decision uncertainty is higher than what is considered within the sponsor's submission.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug[a]	Total costs ($)	Total QALYs	ICER ($ per QALY)
Sponsor's base case	Standard therapy	4,960	0.676	–
	Ranolazine plus standard therapy	6,820	0.752	24,477
Sponsor's corrected base case	Standard therapy	4,861	0.676	–
	Ranolazine plus standard therapy	6,424	0.753	20,201
CADTH reanalysis 1	Standard therapy	4,880	0.676	–
	Ranolazine plus standard therapy	5,943	0.692	65,702
CADTH reanalysis 2	Standard therapy	14,342	0.675	–
	Ranolazine plus standard therapy	14,439	0.752	1,260
CADTH reanalysis 3	Standard therapy	4,309	0.676	–
	Ranolazine plus standard therapy	5,678	0.755	17,303
CADTH reanalysis 4	Standard therapy	4,871	0.676	–
	Ranolazine plus standard therapy	6,443	0.752	20,767
CADTH reanalysis 5	Standard therapy	103,589	14.411	–
	Ranolazine plus standard therapy	136,936	16.046	20,404
CADTH base case (reanalysis 1, 2, 3, 4, and 5)	Standard therapy	287,699	14.372	–
	Ranolazine plus standard therapy	302,780	14.714	44,067

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: Reanalyses are based on publicly available prices of the comparator treatments.

[a] Reference product is the least costly alternative.

Scenario Analysis Results

CADTH undertook several scenario analyses to investigate the impact of utility values, health care resource use costs, and time horizon on the ICER (Table 14). Results of these scenario analyses are presented in Table 15 in Appendix 4.

In the CADTH scenario analyses, adopting an alternative set of health-state utility values (derived from the ERICA trial data with a different mapping approach[14] than the base case) reduced the incremental QALYs (to 0.231), resulting in an increased ICER of $65,109 per QALY for ranolazine plus standard therapy compared with standard therapy. Similarly, adopting an alternative set of health-state resource use costs resulted in an increased ICER for ranolazine compared with standard therapy of $63,719 per QALY, resulting from increased incremental costs associated with ranolazine ($21,890). Using a time horizon of 1 year (i.e., the time horizon originally considered by the sponsor) resulted in an ICER similar to that of the CADTH base case ($44,163 per QALY) with a small level of incremental effectiveness (0.016 QALY, or approximately 5.8 additional days of quality-adjusted life over the course of a year). Given the underlying uncertainty within the clinical evidence, it is difficult to say whether this represents meaningful improvement.

CADTH applied a series of price-reduction analyses to the CADTH base case (Table 16). While the ICER in the CADTH base case is less than $50,000 per QALY, the high level of uncertainty around the comparative effectiveness evidence (and the inability of the model to accurately reflect it) suggests that a higher price reduction is warranted.

Issues for Consideration

- Ranolazine is indicated for use by patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies. The clinical experts consulted by CADTH indicated that ranolazine may also be used by those who are intolerant to standard therapy agents (i.e., calcium-channel blockers, beta-blockers, and long-acting nitrates) and those who are not candidates for revascularization procedures. Clinical experts indicated that this would be a relatively small number of patients compared to those whose symptoms are uncontrolled despite standard therapy. The cost-effectiveness of ranolazine in these patients is unknown.
- The clinical experts consulted by CADTH indicated that other drugs may be used for the treatment of stable angina, despite not having an approved indication, such as ivabradine (Lancora). Ivabradine is indicated for the treatment of stable chronic heart failure with reduced left ventricular ejection fraction (≤ 35%) in adult patients with NYHA class II or III symptoms who are in sinus rhythm with a resting heart rate of at least 77 beats per minute, to reduce the incidence of cardiovascular mortality and hospitalizations for worsening heart failure. Concomitant medication use is also common in this population (e.g., to prevent a cardiovascular event). The clinical effectiveness and cost-effectiveness of ranolazine compared with ivabradine or in combination with other background treatments is unknown.

Overall Conclusions

Based on the CADTH clinical review, the addition of ranolazine to standard therapy for the treatment of stable angina pectoris may reduce the frequency of angina episodes compared to standard therapy alone. However, no statistically significant differences were noted for several other patient-important outcomes (e.g., physical limitation). The sponsor's submitted pharmacoeconomic model was based on the frequency of angina episodes, and no additional patient-important outcomes were included.

CADTH undertook reanalyses to address limitations in the sponsor's submission, including correcting the rate of ranolazine response, correcting health-state resource costs, adopting alternative health-state utility values, and extending the analysis to a lifetime horizon. In CADTH's base-case reanalysis, the addition of ranolazine to standard therapy compared to standard therapy alone was associated with an ICER of $44,067 per QALY. The results must be interpreted with caution as CADTH identified substantial limitations with the submitted economic evaluation that could not be addressed given the model structure. The submitted economic model does not adequately reflect clinician- or patient-important health outcomes and as such the validity of the predicted gains in QALYs is questionable. Further, the sponsor's model inappropriately characterized parameter uncertainty, and the impact of uncertainty on the cost-effectiveness of ranolazine is therefore unknown.

Given the limitations within the clinical evidence — the magnitude of comparative benefits, effects on health-related quality of life, and concerns about its generalizability to the Canadian setting — it is unclear whether the predicted benefits of ranolazine are likely to be realized. These factors, in addition to concerns with the model structure and inputs identified within this report, suggest that the cost-effectiveness of ranolazine is highly uncertain.

Appendix 1: Cost Comparison Tables

The comparators presented in the following tables have been deemed to be appropriate based on feedback from clinical expert(s). Comparators may be recommended (appropriate) practice or actual practice. Costs of comparator products were sourced from the Ontario Drug Benefit[7] (accessed October 2020), unless otherwise specified. Existing product listing agreements are not reflected in the tables and as such the tables may not represent the actual costs to public drug plans.

Table 7: CADTH Cost Comparison Table for Stable Angina Pectoris

Treatment	Strength	Form	Price ($)	Recommended dosage	Daily cost ($)	Annual cost[a] ($)
Ranolazine (Corzyna)	500 mg 1,000 mg	Oral tablet, extended release	3.5000[b]	500 mg twice daily 1,000 mg twice daily	7.00	2,555
Beta-blockers						
Acebutolol (generics)	100 mg 200 mg 400 mg	Tablet	0.0787 0.1177 0.2466	200 mg to 600 mg twice daily	0.16 to 0.35	43 to 129
Atenolol (generics)	25 mg 50 mg 100 mg	Tablet	0.0521[c] 0.1107 0.1821	50 mg to 200 mg daily	0.10 to 0.36	38 to 133
Metoprolol (generics)	50 mg 100 mg	Tablet	0.0624 0.1361	100 mg to 400 mg daily	0.12 to 0.54	45 to 199
	100 mg 200 mg	SR tablet	0.1415 0.2568	100 mg to 400 mg daily	0.14 to 0.51	52 to 187
Nadolol (generics)	40 mg 80 mg 160 mg	Tablet	0.4512 0.3710 1.2046	80 mg to 240 mg daily	0.37 to 1.48	135 to 541
Pindolol (generics)	5 mg 10 mg 15 mg	Tablet	0.1361 0.2323 0.8894	5 mg 3 times daily, up to 40 mg daily	0.41 to 2.01	149 to 734
Propranolol (generics)	10 mg 20 mg 40 mg 80 mg	Tablet	0.0689 0.1107 0.1225 0.2034	10 mg to 20 mg 3 to 4 times daily, up to 400 mg daily	0.21 to o 1.02	75 to 371
Timolol (generics)	5 mg 10 mg 20 mg	Tablet	0.2077 0.3239 0.6304	15 mg to 45 mg daily	0.62 to 1.47	227 to 536
Calcium-channel blockers						
Amlodipine (generic)	2.5 mg 5 mg 10 mg	Tablet	0.0767[d] 0.1343 0.1993	5 mg to 10 mg daily	0.13 to 0.20	49 to 73
Diltiazem (Tiazac)	120 mg 180 mg 240 mg 300 mg 360 mg	ER tablet	0.8956 1.1903 1.5805 1.5760 1.5807	120 mg to 360 mg daily	0.90 to 1.58	327 to 577
Diltiazem (generics)	120 mg 180 mg 240 mg 300 mg	LA capsule	0.3634 0.4824 0.6399 0.7999	120 mg to 360 mg daily	0.36 to 0.96	133 to 352

Treatment	Strength	Form	Price ($)	Recommended dosage	Daily cost ($)	Annual cost[a] ($)
	120 mg 180 mg 240 mg 300 mg 360 mg	SR capsule	0.2133 0.2889 0.3832 0.4720 0.5778	120 mg to 360 mg daily	0.21 to 0.58	78 to 211
Felodipine (generics)	2.5 mg 5 mg 10 mg	ER tablet	0.4050 0.3565 0.5350	2.5 mg to 10 mg daily	0.41 to 0.54	148 to 195
Nifedipine (Adalat XL, generics)	20 mg 30 mg 60 mg	ER tablet	1.2864 0.6171 0.9374	30 mg to 90 mg daily	0.62 to 1.55	225 to 567
Verapamil (generics)	80 mg 120 mg	Tablet	0.2735 0.4250	80 mg 3 to 4 times daily, to 480 mg daily	0.82 to 1.70	299 to 620
Nitroglycerin[e]						
Nitroglycerin (generic)	0.2 mg/h 0.4 mg/h 0.6 mg/h 0.8 mg/h	Patch	0.4686[c] 0.5040 0.5040 0.9178[c]	0.2 to 0.8 mg/h daily	0.47 to 0.92	171 to 335
Nitroglycerin (TriniPatch)	0.2 mg/h 0.4 mg/h 0.6 mg/h	Patch	0.6490[c] 0.7567 0.7567	0.2 to 0.8 mg/h daily	0.65 to 1.51	237 to 552
Nitroglycerin (Transderm-Nitro)	0.2 mg/h 0.4 mg/h 0.6 mg/h	Patch	0.7300[c] 1.0010 1.0010	0.2 to 0.8 mg/h daily	0.73 to 2.00	266 to 730
Nitroglycerin (Minitran)	0.2 mg/h 0.4 mg/h 0.6 mg/h	Patch	0.6574[c] 0.7813 0.7817	0.2 to 0.8 mg/h daily	0.66 to 1.56	240 to 570

ER = extended release; LA = long acting; SR = sustained release.

[a] Annual costs are calculated based on 365 days per year.

[b] Sponsor-submitted price.[1]

[c] Saskatchewan formulary.[21]

[d] Alberta formulary.[22]

[e] Nitroglycerin treatments used in the prevention of stable angina pectoris. Treatments for acute treatment of stable angina pectoris are listed in Table 10.

Table 8: CADTH Cost Comparison Table for Treatments Not Specifically Indicated for Maintenance Treatment of Stable Angina Pectoris

Treatment	Strength	Form	Price ($)	Recommended dosage[a]	Daily cost ($)	Annual cost[b] ($)
Beta-blockers						
Bisoprolol (generics)	5 mg 10 mg	Tablet	0.0715 0.1044	2.5 mg to 20 mg daily	0.04 to 0.21	13 to 76
Carvedilol (generics)	3.125 mg 6.25 mg 12.5 mg 25 mg	Tablet	0.2431 0.2431 0.2431 0.2431	3.125 mg to 25 mg twice daily	0.49	177

Treatment	Strength	Form	Price ($)	Recommended dosage[a]	Daily cost ($)	Annual cost[b] ($)
Labetalol (generics)	100 mg 200 mg	Tablet	0.1983 0.3504	100 mg daily to 600 mg twice daily	0.20 to 2.10	72 to 767
Nebivolol (Bystolic)	2.5 mg 5 mg 10 mg 20 mg	Tablet	1.4107[c]	5 mg daily	1.41	515
Calcium-channel blockers						
Felodipine (generics)	5 mg 10 mg	SR tablet	0.5592 0.8390	2.5 mg to 20 mg daily	0.28 to 1.67	102 to 612
Verapamil (generics)	120 mg 180 mg 240 mg	SR tablet	0.5078[d] 0.5204 0.5075	180 mg daily to 240 mg twice daily	0.52 to 1.02	190 to 370

SR = sustained release.

[a] Based on clinical expert opinion or initial to maximum dose in RxFiles.[23]

[b] Annual costs are calculated based on 365 days per year.

[c] Delta, PA wholesale price September 2020).

[d] Saskatchewan formulary.[21]

Table 9: CADTH Cost Comparison Table for Nitroglycerin Treatments for Acute Treatment of Stable Angina Pectoris

Treatment	Strength	Form	Price ($)	Recommended dosage	Cost per angina event ($)
Nitroglycerin (generics)	0.4 mg	Metered dose spray (200 doses)	8.4600	1 or 2 metered doses, repeated twice at 5- to 10-minute intervals	0.13 to 0.25
Nitroglycerin (Nitrostat)	0.3 mg 0.6 mg	Sublingual tablet	0.1581 0.1581	0.3 mg to 0.6 mg, up to 3 tablets	0.16 to 0.47

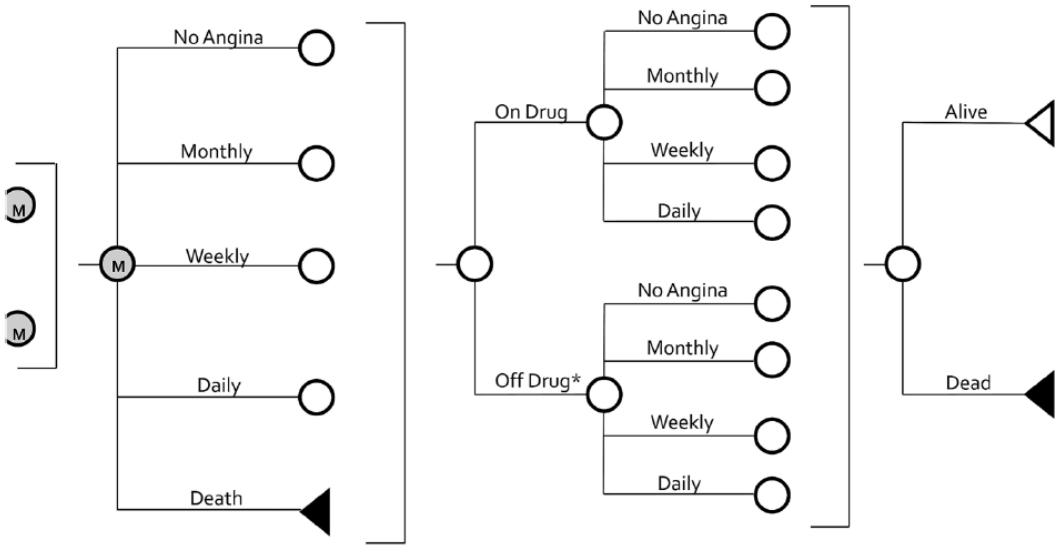
Appendix 2: Submission Quality

Table 10: Submission Quality

Description	Yes	No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	☒	☐	
Model has been adequately programmed and has sufficient face validity	☐	☒	The sponsor's original submission structurally overestimated the response rate of ranolazine and was inconsistent with statements made within the technical report. The model discontinuation function was also inconsistent with the technical report.
Model structure is adequate for decision problem	☐	☒	The model considers the frequency of angina episodes but does not consider the severity of attacks. The model was not considered to adequately reflect clinical decision-making.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	☐	☒	Uncertainty was inappropriately incorporated for most parameters.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	☒	☐	The sponsor was asked to amend an incorrect application of the Dirichlet distribution for probabilities with non-binary outcomes.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	☐	☒	Many aspects of the original submission were the subject of repeated requests for clarification or update. Several important requests were not addressed, limiting CADTH's ability to accurately estimate the cost-effectiveness of ranolazine.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Figure 1: Model Structure



M = Markov node.

Note: Health states were based on Seattle Angina Questionnaire – Angina Frequency scores: 100 = no angina symptoms; 61 to 99 = monthly symptoms; 31 to 60 = weekly symptoms; 0 to 30 = daily symptoms, corresponding to the no angina, monthly angina, weekly angina, and daily angina health states, respectively.

Source: BMJ OPEN, Coleman CI, Freemantle N, Kohn CG, 2015, vol. 5, p. e008861, with permission from BMJ Publishing Group Ltd.; reproduced in the sponsor's submission.[2]

Table 11: Utility Estimates Incorporated in the Model

Health state	Utility	Lower bound	Upper bound
No angina	0.87	0.84	0.90
Monthly angina	0.76	0.75	0.77
Weekly angina	0.65	0.64	0.66
Daily angina	0.54	0.52	0.56

Source: Sponsor's pharmacoeconomic submission.[2]

Detailed Results of the Sponsor's Base Case

Table 12: Disaggregated Summary of Sponsor's Economic Evaluation Results

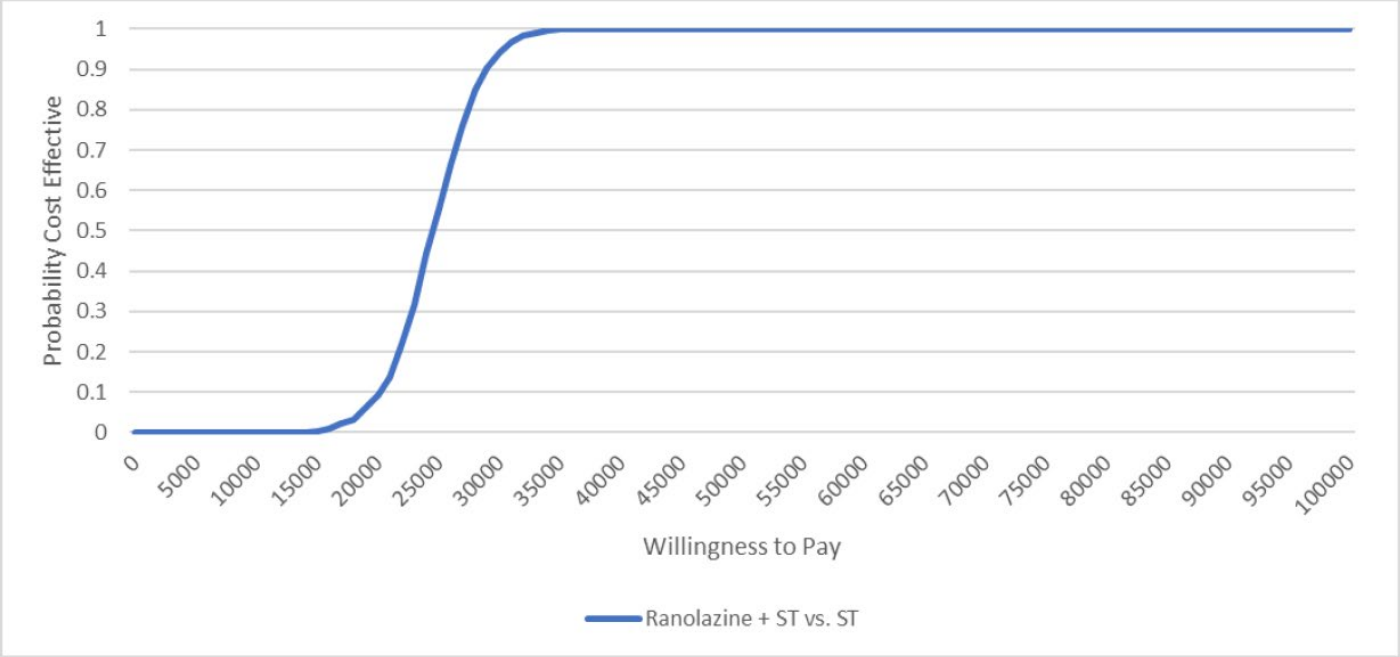
Drug	Standard therapy	Ranolazine plus standard therapy
Discounted LYs		
Total	0.99	0.99
Discounted QALYs		
Total	0.68	0.75
Health state		

Drug	Standard therapy	Ranolazine plus standard therapy
No angina	0.03	0.14
Monthly angina	0.24	0.49
Weekly angina	0.34	0.11
Daily angina	0.001	0.06
Discounted costs ($)		
Total	4,960	6,820
Drug costs	124	2,700
Health-state costs		
No angina	122	518
Monthly angina	1,343	2,741
Weekly angina	2,559	847
Daily angina	812	14

LY = life-year; QALY = quality-adjusted life-year.

Source: Sponsor's pharmacoeconomic submission.[2]

Figure 2: Cost-Effectiveness Acceptability Curve for the Probabilistic Base-Case Analysis



ST = standard therapy.

Source: Sponsor's pharmacoeconomic submission.[2]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Detailed Results of CADTH Base Case

Table 13: Disaggregated Summary of CADTH's Economic Evaluation Results

Parameter	Ranolazine plus standard therapy	Standard therapy	Incremental
Discounted LYs			
Total	21.10	21.10	0
Discounted QALYs			
Total	14.714	14.372	0.342
By health state			
No angina	1.585	0.719	0.865
Monthly angina	5.991	5.135	0.856
Weekly angina	5.875	7.253	−1.378
Daily angina	1.263	1.264	−0.001
Discounted costs ($)			
Total	302,780	287,699	15,081
Drug costs	25,790	573	25,218
By health state			
No angina	12,116	5,500	6,616
Monthly angina	85,969	73,668	12,302
Weekly angina	123,878	152,896	−29,018
Daily angina	55,026	55,063	−37
ICER ($ per QALY)	44,067		

ICER = incremental cost-effectiveness ratio; LY= life-year; QALY = quality-adjusted life-year.

Table 14: CADTH Scenario Analyses

	CADTH base case	CADTH scenario
Scenario analyses		
1. Utility values (alternative mapping approach)	Health-state utility values based on the Goldsmith[6] mapping approach: • Daily angina: 0.54 (0.52 to 0.61) • Weekly angina: 0.65 (0.61 to 0.70) • Monthly angina: 0.76 (0.70 to 0.81) • No angina: 0.87 (0.77 to 0.91)	Health-state utility values based on the based on Wijeysundera[14] mapping approach: • Daily angina: 0.65 (0.61 to 0.69) • Weekly angina: 0.72 (0.68 to 0.76) • Monthly angina: 0.80 (0.75 to 0.85) • No angina: 0.86 (0.84 to 0.92)
2. Utility values (alternative range of possible values)	Utility values from Kohn (2014)[13]: • Daily angina: 0.54 (0.52 to 0.61) • Weekly angina: 0.65 (0.61 to 0.70) • Monthly angina: 0.76 (0.70 to 0.81) • No angina: 0.87 (0.77 to 0.91)	Utility values from Coleman (2015)[5]: • Daily angina: 0.54 (0.52 to 0.56) • Weekly angina: 0.65 (0.64 to 0.66) • Monthly angina: 0.76 (0.75 to 0.77) • No angina: 0.87 (0.84 to 0.90)
3. Health-state resource use costs	Costs reported by Szpakowski (2017)[12]	Costs reported by McGillion (2008)[8]

	CADTH base case	CADTH scenario
4. Ratio of costs between health states	Ratio of costs between health states: • Daily angina: 1 • Weekly angina: 0.58 • Monthly angina: 0.47 • No angina: 0.29.	Ratio of costs between health states: • Daily angina: 1 • Weekly angina: 0.65 • Monthly angina: 0.56 • No angina: 0.42.
5. Time horizon of analysis	Lifetime horizon (40 years)	Sponsor's originally submitted time horizon (1 year)

Note: Reanalyses are based on publicly available prices of the comparator treatments.

Table 15: CADTH Scenario Analyses Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. standard therapy ($ per QALY)
Utility values: Mapping approach					
Standard therapy[a]	285,251	—	15.643	—	—
Ranolazine plus standard therapy	300,272	15,021	15.873	0.231	65,109
Utility values: Range of possible values					
Standard therapy[a]	286,881	—	14.699	—	—
Ranolazine plus standard therapy	301,864	14,984	14.357	0.342	43,841
Health-state resource use costs					
Standard[a] therapy	91,495	—	14.336	—	—
Ranolazine plus standard therapy	113,385	21,890	14.679	0.344	63,720
Ratio of costs between health states					
Standard therapy[a]	340,239	—	14.332	—	—
Ranolazine plus standard therapy	323,557	16,683	14.677	0.346	48,425
Time horizon (1 year)					
Standard therapy[a]	13,503	—	0.676	—	—
Ranolazine plus standard therapy	14,216	713	0.692	0.016	44,163

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

[a] Reference product.

Table 16: CADTH Price Reduction Analyses

	ICERs for ranolazine versus standard therapy ($ per QALY)	
Price reduction	**Sponsor base case**	**CADTH reanalysis**
No price reduction	24,477	44,067
10%	NA	38,375
20%	NA	35,204
30%	NA	29,869
40%	NA	23,824
50%	NA	20,614
60%	NA	14,885
70%	NA	10,872
80%	NA	3,898
90%	NA	693

ICER = incremental cost-effectiveness ratio.

Note: Reanalyses are based on publicly available prices of the comparator treatments.

Appendix 5: Submitted Business Impact Analysis and CADTH Appraisal

Key Take-Aways of the Business Impact Analysis

- No major limitations were identified with the sponsor's base case; as such, the CADTH and sponsor's base case are the same. CADTH explored uncertainty in the proportion of patients eligible for ranolazine in scenario analyses.
- Based on the sponsor's analyses, the expected budget impact of funding ranolazine for the treatment of stable angina is expected to be $21,731,009 in year 1, $62,457,719 in year 2, and $81,992,596 in year 3, with a 3-year budget impact of $166,181,324.
  - Budget impact was sensitive to changes in the rate of first-line treatment failures and the rate of ranolazine uptake.

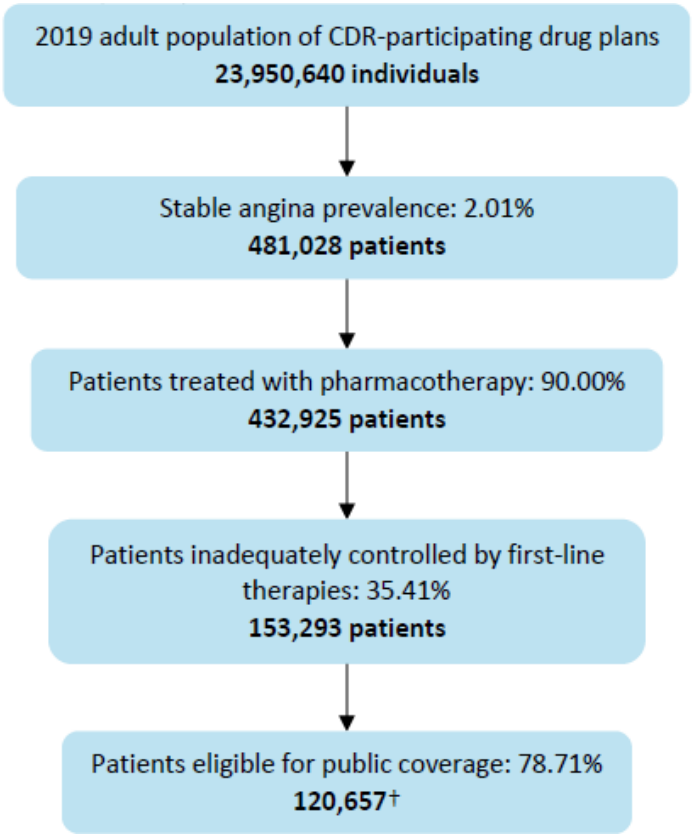
Summary of Sponsor's Business Impact Analysis

In the submitted budget impact analysis[24] (BIA), the sponsor assessed the expected budgetary impact resulting from reimbursing ranolazine as an add-on treatment for adult patients with stable angina pectoris that is inadequately controlled on first-line antianginal therapies (standard therapy). The BIA was undertaken from the perspective of the Canadian public drug plans over a 3-year time horizon, and the sponsor's pan-Canadian estimates reflect the aggregated results from provincial budgets (excluding Quebec), as well as the Non-Insured Health Benefits Program. Key inputs to the BIA are documented in Table 17.

The sponsor estimated the current population using an epidemiologic approach, with the estimated prevalence of stable angina among Canadian adults used to estimate the total number eligible patients (Figure 3). The sponsor assumed that 90% of Canadian adults with stable angina would receive pharmacotherapy and that 35% would be resistant to first-line treatment and therefore be eligible to add on to ranolazine. The sponsor further assumed that 79% of patients would be eligible for public drug-plan coverage.

The sponsor's submission considered a reference scenario in which patients received standard therapy and a new drug scenario in which patients received ranolazine in addition to standard therapy. The cost of ranolazine was based on the sponsor's submitted price ($3.50 per tablet for an annual cost of $2,555 per patient). The sponsor assumed that the cost of standard therapy would be equivalent in both scenarios (i.e., an incremental cost of $0). Thus, the estimated budgetary impact reflects the additional costs associated with the introduction of ranolazine, which would be in addition to the costs currently incurred for standard therapy. The uptake of ranolazine was assumed to be [redacted] in year 1, [redacted] in year 2, and [redacted] in year 3, with the market share of ranolazine assumed to be captured from patients who would otherwise receive standard therapy alone.

Figure 3: Sponsor's Estimation of the Size of the Eligible Population



† Annual growth rate of 1.44% would then be applied to determine the patient pool in each of the years in this analysis.

Source: Sponsor's budget impact analysis submission.[24]

Table 17: Summary of Key Model Parameters

Parameter	Sponsor's estimate
Target population	
Prevalence of stable angina among Canadian adults	2.07%[25]
Proportion of patients who receive pharmacotherapy	90%[a]
Proportion of patients inadequately controlled on first-line therapy	35.41[26]
Proportion of patients eligible for drug-plan coverage	78.71%[b]
Population growth	1.44%[c]
Number of patients eligible for new drug (years 1/2/3)	125,053/126,858/128,691
Market uptake (3 years)	
Uptake (reference scenario) Ranolazine Standard therapy	 0% / 0% / 0% 100% / 100% / 100%
Uptake (new drug scenario) Ranolazine Standard therapy	 [redacted]

Parameter	Sponsor's estimate
Cost of treatment (per patient)	
Cost of annual treatment	
Ranolazine	$2,557
Standard therapy	$0[d]

[a] Sponsor's assumption, based on expert opinion.

[b] Sponsor's assumption, based on the assumption that 50% of patients at least 65 years of age would have full access to public drug coverage, while the other 50% of patients would have access reflective of the coverage rates for adult patients less than 65 years of age in each jurisdiction.

[c] Drug-plan adult population growth; source not referenced by the sponsor.

[d] The sponsor assumed that all eligible patients in both treatment arms would be receiving standard therapy and excluded costs associated with standard therapy from the analysis.

Summary of the Sponsor's Budget Impact Analysis Results

The estimated budget from the drug-plan perspective of reimbursing ranolazine as an add-on treatment for patients whose stable angina remains uncontrolled on standard therapy is expected to be $21,731,009 in year 1, $62,457,719 in year 2, and $81,992,596 in year 3, with a 3-year budget impact of $166,181,324.

In the sponsor's scenario analyses, assuming an increased proportion of first-line treatment failures and increased uptake of ranolazine resulted in 41% and 25% increased costs, respectively, over 3 years.

CADTH Appraisal of the Sponsor's Budget Impact Analysis

CADTH identified the following key limitation of the sponsor's analysis that may have a notable implication on the results of the BIA:

- **The proportion of patients eligible for ranolazine reimbursement may be underestimated.** In its BIA, the sponsor estimated that 79% of patients prescribed ranolazine would be eligible for public drug-plan coverage.[24] This assumption was based on the distribution of patients in the CARISA trial,[15] in which approximately half were aged 65 years and older. The sponsor assumed that patients aged less than 65 years would have "access reflective of the coverage rates for adult patients younger than 65 years of age in each jurisdiction," which ranged from 20% to 100% depending on jurisdiction.[27] Considering that the mean age of participants in the ERICA trial[3] was approximately 62 years, it may be reasonable to consider that a higher proportion of patients would receive public coverage.

  Ranolazine is indicated for use by patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies. The sponsor's BIA considers the use of ranolazine only among those who are inadequately controlled by first-line treatments.[24] While ranolazine may also be used by those who are intolerant to standard therapy agents (i.e., calcium-channel blockers, beta-blockers, and long-acting nitrates) and those who are not candidates for revascularization procedures, the clinical experts consulted by CADTH indicated that this would be a relatively small number of patients compared to those whose symptoms are uncontrolled despite standard therapy.

  The sponsor assumed that approximately 35% of patients with stable angina would experience a first-line treatment failure.[24] This estimate was adopted from the RITA-2 trial,[26] in which 182 of 514 (35%) patients with coronary artery disease randomized to continued medical therapy eventually required surgical revascularization. Approximately 80% of patients in RITA-2 had stable angina at baseline, and 53% were classified as having CCS grade II or worse angina.[28] In its scenario analyses, the sponsor adopted an alternative proportion of first-line treatment failures (50%) from the ISCHEMIA trial, which randomized patients with stable coronary disease to invasive treatment (e.g., coronary

catherization, coronary artery bypass grafting, percutaneous coronary intervention) or to conservative management (i.e., secondary prevention of cardiovascular events with lifestyle and pharmacologic interventions [antiplatelets, statins, antihypertensive drugs, and anti-ischemic drugs]). Notably, patients with "unacceptable" angina despite "maximum acceptable doses" of medical therapy were excluded from the ISCHEMIA trial, and standard first-line treatments for stable angina (i.e., beta-blockers, calcium-channel blockers, and long-acting nitroglycerin) were not utilized.

  - In scenario analyses, CADTH explored the impact of public drug-plan coverage rates and the proportion of first-line treatment failure.

- Additional limitations were identified but were not considered to be key limitations. These limitations include not considering treatment discontinuation, not considering drug costs to treat adverse events, and assuming that standard therapy costs would not change with the addition of ranolazine.
  - **Treatment discontinuation was not considered.** The sponsor's BIA submission did not consider the impact of treatment discontinuation on the budget impact of reimbursing ranolazine. While the real-world long-term discontinuation of ranolazine is uncertain, up to 40% of patients in the CARISA trial[15] had discontinued ranolazine by the end of the second year. Discontinuation of ranolazine would be expected to reduce the costs of reimbursing ranolazine; however, patients who discontinue ranolazine may require further intervention or treatment.
  - **Costs to treat adverse events were not considered.** The sponsor's BIA submission did not consider the costs to treat adverse events associated with ranolazine or standard therapy. As noted in the clinical review, 27% to 40% of participants who received ranolazine in the ERICA,[3] CARISA,[15] and TERISA[17] trials experienced adverse events; however, these trials were 6 to 12 weeks in duration and the reporting of harms data was poor. Serious adverse events were relatively rare and would not be expected to add substantial costs to the estimated budget impact of reimbursing ranolazine.
  - **Standard therapy costs were considered to be equivalent in both the ranolazine and standard therapy arms:** The submitted BIA assumed that ranolazine would be added to standard therapy and that standard therapy would be applied equally in the presence and absence of ranolazine (i.e., the cost of standard therapy would not change).[24] The clinical experts consulted by CADTH indicated that, for patients taking ranolazine in addition to standard therapy, the composition and dosage of standard therapy would be determined on an individual patient basis, with a potential reduction in the dosage of background treatments for patients who had previously experienced an adverse event with standard therapy. The annual cost of the background treatments (i.e., beta-blockers, calcium-channel blockers, and long-acting nitroglycerine) is relatively low, and changes to the background treatments would not be expected to have a large impact on the estimated budget impact of reimbursing ranolazine.

CADTH Reanalyses of the Budget Impact Analysis

CADTH did not undertake reanalysis of the sponsor's BIA. The base-case analysis remained unchanged from the sponsor's base case and is presented in Table 18. Based on the BIA base case, the expected budget impact for funding ranolazine for the treatment of stable angina is expected to be $21,731,009 in year 1, $62,457,719 in year 2, and $81,992,596 in year 3, for a 3-year budget impact of $166,181,324.

Scenario analyses were conducted using the sponsor's base case. Increasing the proportion of patients who experience a first-line treatment failure had the greatest impact on the results (41% increase, to $234,662,638 over 3 years) (Table 18).

Table 18: Detailed Breakdown of the CADTH Scenario Analyses of the BIA

Analyses	Scenario	Year 0 (current situation) ($)	Year 1 ($)	Year 2 ($)	Year 3 ($)	3-year total ($)
BIA base case (unchanged)	Reference	0	0	0	0	0
	New drug	0	21,731,009	62,457,719	81,992,596	166,181,324
	Budget impact	0	21,731,009	62,457,719	81,992,596	166,181,324
CADTH sensitivity analysis 1: 100% of patients covered by public drug plans	Reference	0	0	0	0	0
	New drug	0	27,564,787	79,221,074	103,994,275	210,780,136
	Budget impact	0	27,564,787	79,221,074	103,994,275	210,780,136
CADTH sensitivity analysis 2: Increased proportion of first-line treatment failures (50%)	Reference	0	0	0	0	0
	New drug	0	30,686,095	88,195,790	115,780,754	234,662,638
	Budget impact	0	30,686,095	88,195,790	115,780,754	234,662,638

BIA = budget impact analysis.

References

1. CDR submission: Corzyna (ranolazine), 500 and 1000 mg extended-release tablets for oral administration [CONFIDENTIAL sponsor's submission]. Mississauga (ON): Kye Pharmaceuticals Inc.; 2020 Sep.
2. Pharmacoeconomic evaluation. In: CDR submission: Corzyna (ranolazine), 500 and 1000 mg extended-release tablets for oral administration [CONFIDENTIAL sponsor's submission]. Mississauga (ON): Kye Pharmaceuticals Inc.; 2020 Sept
3. Stone PH, Gratsiansky NA, Blokhin A, Huang IZ, Meng L, Investigators E. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. *J Am Coll Cardiol.* 2006;48(3):566-575.
4. Corzyna (ranolazine), 500 and 1000 mg extended-release tablets for oral administration [draft product monograph]. Mississauga (ON): Kye Pharmaceuticals Inc.; 2020 Mar 29.
5. Coleman CI, Freemantle N, Kohn CG. Ranolazine for the treatment of chronic stable angina: a cost-effectiveness analysis from the UK perspective. *BMJ Open.* 2015;5(11):e008861.
6. Goldsmith. Mapping of the EQ-5D index from clinical outcome measures and demographic variables in patients with coronary heart disease. *Health and Quality of Life Outcomes.* 2010.
7. Ontario Ministry of Health Long-Term C. Ontario drug benefit formulary/comparative drug index. 2019; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2020 October 30.
8. McGillion M, Croxford R, Watt-Watson J, LeFort S, Stevens B, Coyte P. Cost of illness for chronic stable angina patients enrolled in a self-management education trial. *Canadian Journal of Cardiology.* 2008;24(10):759-764.
9. Bank of Canada. Inflation calculator. 2019; https://www.bankofcanada.ca/rates/related/inflation-calculator/. Accessed 2020 Oct 7.
10. Campeau Lucien. Grading of angina pectoris. *Circulation.* 1976;54:5223.
11. Arnold SV, Morrow DA, Lei Y, et al. Economic impact of angina after an acute coronary syndrome: insights from the MERLIN-TIMI 36 trial. *Circ Cardiovasc Qual Outcomes.* 2009;2(4):344-353.
12. Szpakowski N, Qiu F, Masih S, Kurdyak P, Wijeysundera HC. Economic Impact of Subsequent Depression in Patients With a New Diagnosis of Stable Angina: A Population-Based Study. *J Am Heart Assoc.* 2017;6(10).
13. Kohn CG. Impact of angina frequency on health utility values of patients with chronic stable angina. 2014.
14. Wijeysundera HC, Tomlinson G, Norris CM, Ghali WA, Ko DT, Krahn MD. Predicting EQ-5D utility scores from the Seattle Angina Questionnaire in coronary artery disease: a mapping algorithm using a Bayesian framework. *Med Decis Making.* 2011;31(3):481-493.
15. Chaitman BR, Pepine CJ, Parker JO, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. *JAMA.* 2004;291(3):309-316.
16. Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa (ON): CADTH; 2017: https://www.cadth.ca/dv/guidelines-economic-evaluation-health-technologies-canada-4th-edition. Accessed 1800 Mth Dd.
17. Kosiborod M, Arnold SV, Spertus JA, et al. Evaluation of ranolazine in patients with type 2 diabetes mellitus and chronic stable angina: results from the TERISA randomized clinical trial (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina). *J Am Coll Cardiol.* 2013;61(20):2038-2045.
18. Morrow DA. Effects of Ranolazine on Recurrent Cardiovascular Events in Patients With Non–ST-Elevation Acute Coronary Syndromes: The MERLIN-TIMI 36 Randomized Trial. 2007.
19. Spertus JA, Jones P, McDonell M, Fan V, Fihn SD. Health status predicts long-term outcome in outpatients with coronary disease. *Circulation.* 2002;106(1):43-49.
20. Ranolazine (Ranexa®) for chronic stable angina [Issues in Emerging Health Technologies]. Ottawa (ON): CADTH; 2007: https://cadth.ca/sites/default/files/pdf/E0022_Ranolazine_Chronic_Angina_cetap_e.pdf. Accessed Oct 7 2020.
21. Saskatchewan Drug Plan. Regina (SK): Government of Saskatchewan, Ministry of Health: http://formulary.drugplan.ehealthsask.ca/SearchFormulary. Accessed 2020 October 30.
22. Interactive drug benefit list. Edmonton (AB): Alberta Health; 2019: https://idbl.ab.bluecross.ca/idbl/load.do. Accessed 2020 October 30.
23. RxFiles. Angina: Treatment Overview. 2020: https://www.rxfiles.ca/RxFiles/uploads/documents/members/Cht-angina.pdf. Accessed October 7, 2020.
24. Budget Impact Analysis: Corzyna (ranolazine), 500 and 1000 mg extended-release tablets for oral administration [CONFIDENTIAL sponsor's submission]. 2020.
25. Chow. Regional variation in self-reported heart disease prevalence in Canada. 2005.
26. Henderson RA, Pocock SJ, Clayton TC, et al. Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. *Journal of the American College of Cardiology.* 2003;42(7):1161-1170.

27. Understanding the gap: A pan-canadian analysis of prescription drug insurance coverage. Ottawa (ON): Conference Board of Canada; 2017: https://www.conferenceboard.ca/e-library/abstract.aspx?did=9326&AspxAutoDetectCookieSupport=1. Accessed 2020 Oct 7.

28. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. *The Lancet*. 1997;350(9076):461-468.