CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

RANOLAZINE (CORZYNA — KYE Pharmaceuticals Inc.)
Indication: Patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that ranolazine not be reimbursed 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, including beta-blockers and calcium channel blockers.

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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.

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Recommendation

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Reasons for the Recommendation

1. CDEC reviewed 3 key randomized controlled trials (RCTs: ERICA, CARISA, and TERISA) of ranolazine 1,000 mg twice daily in patients with coronary artery disease and stable angina pectoris. In the ERICA study, the average number of angina episodes per week was reduced to 2.9 (standard error [SE] 0.19) events per week in the ranolazine group, compared with 3.3 (SE 0.22) events per week in the placebo group (P = 0.028). In the TERISA study, the least squares (LS) mean weekly number of angina episodes was reduced to 3.8 [95% confidence interval (CI), 3.6 to 4.1] and 4.3 (95% CI, 4.0 to 4.5) episodes per week for the ranolazine and placebo groups, respectively (P = 0.008). In the CARISA study, ranolazine improved exercise duration on a modified Bruce protocol exercise test relative to placebo with a LS mean difference of 24.0 seconds (SE 11.0, P = 0.03) for the change from baseline measured at trough drug levels. Although results of these trials suggested that ranolazine 1,000 mg twice daily as add-on to standard antianginal drugs reduced angina frequency or improved exercise duration relative to placebo plus standard treatments, the magnitude of benefit on these outcomes was of unclear clinical significance. Further, the key studies were associated with significant limitations, which contribute to the uncertainty in their results. For ERICA and CARISA, uncertainty is also due to significant gaps in the reporting of study methodology, statistical analysis plan, patient characteristics, disposition, and results. The generalizability of the TERISA study is uncertain as the study enrolled an enriched population that were demonstrated to be adherent to the study drug and outcome reporting.
2. CDEC noted that recurrent and sustained angina symptoms would be expected to have an impact on a patient's health-related quality of life (HRQoL) and that an improvement in HRQoL is an important outcome of treatment response in Canadian clinical practice. HRQoL was assessed as a secondary outcome in 2 key studies (ERICA and TERISA). No differences were found between ranolazine and placebo on the disease perception/quality of life domain of the Seattle Angina Questionnaire (SAQ) in the ERICA study, and although there were statistical differences detected in the angina frequency domain, CDEC was unable to draw any conclusions about the clinical relevance of this outcome as there is uncertainty regarding the accepted minimum important difference (MID). No statistically significant differences were found between groups on the change from baseline in the Short Form (36) Health Survey (SF-36) physical component score and mental component score in the TERISA study. Overall, based on the evidence reviewed, the potential benefit of ranolazine on HRQoL remains uncertain.
3. The pharmacoeconomic model submitted by the sponsor was associated with substantial limitations including a lack of sufficient comparative clinical evidence, the inability to reflect disease severity, the relationship between angina frequency and health state utility, and insufficient data to inform treatment response rates. CADTH was unable to address these important limitations. Hence, the cost-effectiveness of ranolazine for the treatment of stable angina remains highly uncertain. CADTH was unable to provide an estimate of the cost-effectiveness of ranolazine for this indication.

Discussion Points

- CDEC discussed that the results of the ERICA, CARISA, and TERISA trials may not be generalizable to Canadian patients with inadequately controlled stable angina. The trials were conducted between 1999 and 2005, and most patients in the ERICA and TERISA studies were from Eastern Europe; therefore, the management of coronary artery disease may not have been optimized according to current Canadian practice standards for that indication.
- Given the overall modest clinical benefit of ranolazine on angina frequency and exercise tolerance observed in the ERICA, CARISA, and TERISA studies, it is unlikely that ranolazine is an effective treatment option for many patients who continue to experience significant angina symptoms despite treatment with antianginal therapies. Furthermore, based on the available evidence, the incremental benefit of ranolazine in patients on optimized doses of standard antianginals is unknown. CDEC heard from clinical experts that there is potential that ranolazine may benefit some patients; however, CDEC was unable to identify such populations based on the evidence reviewed.

- None of the key trials evaluated the efficacy or safety of ranolazine 500 mg twice daily dose regimen; this was identified as an evidence gap.
- CDEC discussed that ranolazine has clinically relevant drug interactions with other medications often prescribed in patients with cardiac disease, including metformin, simvastatin, lovastatin, diltiazem, verapamil, and digoxin. Concurrent use with CYP3A4 inducers or strong inhibitors of CYP3A4 and class IA or class III antiarrhythmics is contraindicated, and the product monograph includes precautions for use with moderate CYP3A4 inhibitors, P-glycoprotein inhibitors and drugs metabolized by CYP2D6. Due to the QT prolongation associated with ranolazine, the product monograph contains warnings regarding concurrent use with other drugs or for conditions that may increase the risk of clinically significant arrhythmias.
- When interpreting CADTH's pharmacoeconomic reanalysis, it is important to note that the uncertainty around the estimate of the incremental cost-effectiveness ratio is driven primarily by uncertainty around treatment effectiveness. The limitations identified within CADTH's appraisal do not affect the cost attributable to the purchase of ranolazine ($25,218 per patient over a 40-year time horizon). As a result, the estimate of the incremental cost-effectiveness ratio within CADTH's reanalysis should be interpreted with caution, as the true value of the incremental cost-effectiveness ratio for ranolazine may be much higher.

Background

Ranolazine has a Health Canada indication for use 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, including beta-blockers and calcium channel blockers. Ranolazine is available as a 500 mg and 1,000 mg extended release tablet. The recommended initial dose is 500 mg twice daily, which may be increased to 1,000 mg twice daily, as needed, based on clinical symptoms.

Ranolazine was approved in the US in 2006 for the treatment of chronic angina, with a recommended dose of 500 mg or 1000 mg twice daily. In Europe, ranolazine was approved for use 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). It is available as 375 mg, 500 mg and 750 mg prolonged-release tablets, with a recommended dose of 375 mg to 750 mg twice daily. Prior to approval in Canada, ranolazine was available via Health Canada's Special Access Programme.

Summary of Evidence Considered by CDEC

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

Summary of Patient Input

No patient groups provided input for this submission.

Clinical Trials

The systematic review included 3 key trials and 5 other randomized trials in patients with angina. The key trials (ERICA, CARISA, and TERISA) were multicenter, randomized, double-blind, parallel design trials that compared ranolazine 1,000 mg twice daily to placebo, in addition to background antianginal drugs. The trials enrolled 565 to 949 patients with stable angina and ranged in duration from 6 to 12 weeks.

Of 5 other trials, 4 were double blind and 1 was open label; 3 used a parallel design and 2 were crossover studies. The studies enrolled 29 to 2,651 patients with stable angina who received ranolazine 500 mg to 1,500 mg twice daily compared with placebo or usual care (as add-on to background antianginal drugs in 4 trials, monotherapy in 1 trial). The treatment duration ranged from 1 week to 1.8 years.

This submission was based on third party data (i.e., publicly available information). CDEC focused on the results of the 3 key RCTs (ERICA, CARISA and TERISA studies), as the 5 other included studies had issues associated with the study design, population, sample size, outcomes measures or other sources of bias, that limited the utility or robustness of the findings.

There were major and significant gaps in the reporting of study methodology, statistical analysis plan, patient characteristics, disposition, and results in the pivotal studies (ERICA and CARISA) which made it difficult to assess their internal and external validity. Data are lacking comparing ranolazine with other antianginal treatment options as the control treatment in all trials was placebo or usual care. None of the key trials included a 500 mg twice daily dose group. The key trials were of short duration (up to 12 weeks) and reporting of harms was incomplete in all trials.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, CDEC discussed the following: angina frequency, nitroglycerin use, exercise duration, and HRQoL. The primary outcome in the key trials was self-reported angina frequency in the ERICA and TERISA studies, and the change from baseline in exercise duration measured at trough drug levels (12 hours after dose) in the CARISA study.

- Angina frequency and nitroglycerin use was based on the self-reported number of angina events or nitroglycerin doses consumed and were analyzed as the average number of events or doses per week.
- Exercise duration was analyzed as the time to onset of angina or electrocardiogram ischemia on a modified Bruce protocol exercise test.
- HRQoL was assessed using the SAQ and SF-36.
- The SAQ is a 19-item self-reported instrument that includes 5 dimensions: angina frequency, physical limitation, angina stability, disease perception/quality of life, and functioning. Each domain is scored between 0 and 100, with higher numbers representing higher functioning. A MID of 10 points has been reported.
- The SF-36 is a general health status questionnaire that includes 8 domains and 2 component summaries, which are derived from aggregating the 8 domains according to a scoring algorithm. The component scores range from 0 to 100 with higher scores indicating better health status. The MID for either the physical or mental component summary score has been reported to be between 2.5 points and 5 points.

Efficacy

The frequency of self-reported angina episodes was lower among patients who received ranolazine 1,000 mg twice daily versus placebo (as add-on to background antianginal drugs) in the 3 key trials, with differences that were statistically significant in the ERICA and TERISA studies. During the 6-week double-blind treatment period in the ERICA study, the average number of angina episodes per week was reduced from a baseline trimmed mean of 5.6 or 5.7 events per week, to 2.9 (standard error [SE] 0.19) events per week in the ranolazine group, compared with 3.3 (SE 0.22) events per week in the placebo group (P = 0.028). In the TERISA study, the LS mean weekly number of angina episodes was 6.6 and 6.8 at baseline, and during the 6-week double-blind treatment period was 3.8 [95% confidence interval (CI), 3.6 to 4.1] and 4.3 (95% CI, 4.0 to 4.5) episodes per week for the 1,000 mg ranolazine and placebo groups, respectively (P = 0.008).

Self-reported nitroglycerin use was lower during treatment with ranolazine versus placebo, with 2.0 (SE 0.20) versus 2.7 (SE 0.22) trimmed mean doses per week in the ERICA study (P = 0.014), and 1.7 (95% CI, 1.6 to 1.9) versus 2.1 (95% CI, 1.9 to 2.3) mean weekly doses (P = 0.003) for ranolazine versus placebo, respectively, in the TERISA study.

Ranolazine 1,000 mg twice daily plus background antianginal drugs improved exercise duration on a modified Bruce protocol exercise test relative to placebo plus background therapy, with a LS mean difference of 24.0 seconds (SE 11.0, P = 0.03) for the change from baseline measured at trough drug levels (CARISA study).

Two studies (ERICA and TERISA) reported data on HRQoL using the SAQ and Short Form (36) Health Survey (SF-36); however, these outcome measures had limitations, and thus the impact of ranolazine on HRQoL is uncertain.

Harms (Safety)

Among those enrolled in the 3 key trials, 27% to 40% who received ranolazine 1,000 mg, and 22% to 35% who received placebo, experienced adverse events during the 6 to 12 week studies. Nausea, dizziness, and constipation occurred more frequently among those who received ranolazine than placebo in all 3 studies.

The frequency of withdrawal due to adverse events was low (1% to 2%) and similar between groups in the ERICA and TERISA studies. In the CARISA study, more patients in the ranolazine 1,000 mg group withdrew due to adverse events than placebo (9% versus 5%).

Serious adverse events were reported in 3.4% of patients in the ranolazine and 4.2% of those in the placebo group in the TERISA study, and in 1.8% versus 2.1% in the ranolazine 1,000 mg group versus placebo in the ERICA study. The CARISA study did not report the overall frequency of serious adverse events, but an integrated safety review of phase II and III trials conducted by the FDA reported serious adverse events in 5.4% of patients who received ranolazine (56 of 1,030 patients) compared with 3.0% who received placebo (22 of 738 patients).

Indirect Treatment Comparisons

No indirect treatment comparisons were submitted by the sponsor and no relevant published reports were identified in the literature search conducted by CADTH.

Cost and Cost-Effectiveness

Ranolazine is available as a 500 mg and 1,000 mg tablet, at a submitted price of $3.50 per tablet (regardless of the dose). The recommended initial dosage is 500 mg twice daily. The annual per patient drug acquisition cost of ranolazine is $2,555.

The sponsor submitted a cost-utility analysis of ranolazine as an add-on to standard therapy compared to standard therapy alone 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. The sponsor's analysis was conducted from the perspective of a Canadian publicly funded health care payer over a one-year time horizon. The pharmacoeconomic submission was based on a Markov model which comprised 4 health states related to the frequency of angina symptoms (Monthly Angina, Weekly Angina, Daily Angina, and No Angina) and death. The relative treatment effects (i.e., the frequency of angina symptoms) of ranolazine and standard therapy, as well as characteristics of the modelled cohort, were based on the ERICA trial.

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

- There was considerable uncertainty in the underlying clinical evidence, including the strength of comparative effectiveness, the effect on HRQoL, and the representativeness of the pivotal trial population to a Canadian patient population.
- The sponsor's pharmacoeconomic model does not adequately reflect the clinical management of angina. Treatment effectiveness was modelled in terms of a reduction in the frequency of angina symptoms, while in clinical practice treatment decisions may be made based on reductions in symptom severity, both in addition to and irrespective of the frequency of episodes.
- The estimated rate of response (i.e., the proportion of patients who have a reduced frequency of episodes) to ranolazine was overestimated.
- The sponsor's approach to estimating angina management costs was not consistent with CADTH guidelines, resulting in costs being overestimated.
- The health state utility values for the model health states are uncertain owing to the mapping approach used.
- Treatment discontinuation was not modelled in a manner consistent with data observed in long-term studies.

While CADTH undertook reanalysis to address the identified limitations (including reducing the rate of ranolazine response, adopting alternative health state costs, considering a wider range of possible utility values, and extending the analysis horizon to lifetime), the impact of angina severity could not be addressed given the model design. Owing to methodologic limitations with the sponsor's submitted model, the cost-effectiveness of ranolazine remains highly uncertain for this indication.

CDEC Members

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

January 20, 2021, Meeting (Initial)

Regrets

One CDEC member did not attend.

Conflicts of Interest

None

May 19, 2021 Meeting (Reconsideration)

Regrets

One CDEC member did not attend.

Conflicts of Interest

None