Ranolazine (Ranexa™)
CV Therapeutics, Inc.

For the treatment of stable angina.¹

The US Food and Drug Administration (FDA) issued an “approvable” letter in October 2003 for the use of Ranexa™ in the treatment of chronic angina. The letter indicated that ranolazine is an effective anti-anginal drug, but that additional clinical information was needed before it could be approved.¹ In December 2003, the Cardiovascular and Renal Drugs Advisory Committee met to review the literature and to evaluate some unanswered questions about safety, though no formal vote was held.²,³ An electronic transcript of the meeting highlights the matters that require clarification.⁴

The anti-anginal action of ranolazine may be related to the inhibition of partial fatty oxidase (pFOX). By blocking the beta oxidation of fatty acids, the heart’s metabolism shifts to produce more energy in the form of adenosine triphosphate (ATP) from glucose.⁵ Since glucose requires less oxygen to generate the same amount of energy as fatty acids, this can be advantageous in the presence of ischemia.

Pharmacokinetic data are limited. It has been stated that ranolazine has a short half-life (approximately two hours) after oral administration. Consequently, a sustained-release (SR) formulation was developed and is being investigated. Ranolazine, which is metabolized by the liver, can be affected by cytochrome P450 isoenzyme inducers or inhibitors. Elucidation of its drug interaction profile is required.⁵

Ranolazine 375 mg and 500 mg formulations were submitted for FDA review, with a proposed initial dosage of 500 mg twice daily, increasing as required to 750 mg or 1,000 mg twice daily. The manufacturer intends to market the SR formulation.⁴

In Canada, more than $18 billion was spent treating cardiovascular disease in 1998. In 2001, it was estimated that one in 10 Canadians visited a physician for a cardiovascular complaint, with 16% of these related to ischemic heart disease, including angina.⁶

Chronic stable angina manifests as chest pain, typically as a predictable response to stress such as exercise or emotion.⁷ It is commonly treated with fast or long-acting nitrates, beta blockers and calcium channel antagonists.⁸ Other medications, tailored to an individual patient and his or her risk factors, may be used to reduce morbidity and mortality (e.g., Aspirin, lipid lowering therapy, angiotensin-converting enzyme inhibitors). A discussion of the management of chronic stable angina has been published by the American College of Cardiology and the American Heart Association.⁸
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Cost: A cost for ranolazine was unavailable at the time of this review.

Evidence: Several published, randomized, placebo-controlled studies examined the role of ranolazine in the treatment of chronic stable angina.9-12 The immediate-release formulation was used in two trials by Thadani and Pepine.11,12 Thadani et al. failed to show a benefit for exercise duration, time to ST-segment depression and time to onset of angina, but this was due to an insufficient dose.11 The Pepine et al. trial showed anti-anginal effects at peak serum levels, but these effects were lost at serum trough levels. This may have been due to the short duration of action of the immediate-release formulation.12

The SR formulation was used in two phase III trials: MARISA (Monotherapy Assessment of Ranolazine in Stable Angina) and CARISA (Combination Therapy Assessment of Ranolazine in Stable Angina).9,10

In the recently published MARISA trial, 191 patients were randomized to receive 500 mg, 1,000 mg or 1,500 mg ranolazine SR or placebo twice daily for one week according to a four period crossover design.9 Of the patients, 168 (88%) completed all four crossover periods. Patients were not receiving anti-anginal therapy other than sublingual nitroglycerin as needed. End points included exercise duration (peak and trough serum levels), time to angina and time to 1 mm ST-segment depression. Therapy with ranolazine was statistically superior compared with placebo for all three end points. Subgroup analyses were performed according to diabetes, gender, history of heart failure and age. There were no significant differences between the subgroups and the overall population. In an open-label extension of the MARISA trial, the one-year and two-year survival rates on ranolazine were 96.3% and 93.6% respectively. Most patients (>70%) received 1,000 mg ranolazine twice daily.9 Another sub-analysis of the trial suggested that benefits were maintained in elderly patients and in patients with co-morbid congestive heart failure (CHF) and diabetes.13-15

In the CARISA study,10 patients (n=823) were randomized to receive placebo or ranolazine SR 750 mg or 1,000 mg twice daily for 12 weeks. They were stratified according to the anti-anginal medication that they were receiving at the time of enrolment (i.e., atenolol 50 mg daily, diltiazem 180 mg daily or amlodipine 5 mg daily). The primary end point was the effect of ranolazine on treadmill exercise ability (at serum trough levels). Secondary efficacy end points included exercise duration at peak serum levels (i.e. four hours post-dose), time to angina and time to 1 mm ST-segment depression. The number of angina attacks and the use of sublingual nitroglycerin were also recorded.

At 12 weeks, exercise duration increased with ranolazine use (p=0.03 trough, p<0.02 peak). Mean weekly angina attacks were significantly less frequent with ranolazine. The survival rates of patients who received ranolazine during the trial or during the open-label follow-up (n=750) were 98.4% at year 1 (95% CI: 97.4% to 99.5%) and 95.9% at year 2 (95% CI: 94.0% to 97.7%).10
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A summary of the clinical trial data was published. A bibliography of publications regarding animal and human studies may be found on the CV Therapeutics, Inc. website. The transcript of the December 2003 meeting of the Cardiovascular and Renal Drugs Advisory Committee highlights the data’s perceived weaknesses and strengths, based on restricted and unrestricted approval in chronic angina.

In the MARISA trial, adverse events generally increased with higher doses: 15.6%, 16.0%, 21.7% and 34.2% for patients receiving placebo, 500 mg, 1,000 mg and 1,500 mg ranolazine respectively. Dizziness, nausea, asthenia and constipation were the most frequent adverse events reported. There was some increase in the QTc interval, but no patient discontinued participation because of QTc prolongation. A subgroup analysis revealed that patients with comorbid diseases such as CHF or diabetes experienced a similar frequency and pattern of adverse effects. Elderly patients (>65 years) experienced a higher rate of adverse events. The FDA’s website presents more data on ranolazine’s safety profile, with an emphasis on the electrophysiological effects.

In the CARISA trial, the most commonly reported dose-related side effects were constipation, dizziness, nausea and asthenia. Five patients experienced syncope in the 1,000 mg dose group; all recovered without sequelae. The QTc interval seemed to increase in those patients receiving ranolazine; mean QTc was 421.5, 427.6 and 430.7 milliseconds at three months (p<0.001). Torsades de pointes was not evident.

Ranolazine has been investigated as monotherapy and as combination therapy in patients with stable angina. Both trials demonstrate significant anti-anginal efficacy, but several questions regarding the dose, target population and safety remain unanswered. The lack of dose-response data and the evidence of a prolonged QTc interval with higher doses warrant further investigation. The ideal patient population must be defined as to whether ranolazine should be restricted to a particular group of patients. Ranolazine’s tolerability and efficacy profile at therapeutic doses over the longer term requires further study, possibly with other anti-anginal agents.

References:


This series highlights medical technologies that are not yet in widespread use in Canada and that may have a significant impact on health care. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada. These summaries have not been externally peer reviewed.

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