

# NEW DRUG EVALUATION

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## RANOLAZINE

Ranolazine is an adjunctive therapy licensed for use in patients with stable angina that remains inadequately controlled despite treatment with first-line anti-anginal agents such as beta-blockers, calcium-channel blockers and nitrates. Placebo-controlled studies have demonstrated modest improvements in exercise time and in the frequency of angina attacks, although these studies did not use optimised / maximal background anti-anginal therapy. The limited data available means that its place in therapy remains uncertain, and as QT-prolongation and drug interactions are important potential hazards, prescribing of ranolazine should be initiated by cardiologists only.

### What is it?

Ranolazine modified-release (MR) tablets (Ranexa®, CV therapeutics) are licensed as an adjunctive anti-anginal treatment for patients with symptomatic stable angina pectoris who are inadequately controlled or intolerant to first-line anti-anginal therapies.<sup>1</sup> The recommended initial dose is 375 mg twice daily, which may be increased to 500 mg twice daily after two to four weeks, and further titrated to the maximum recommended dose of 750 mg twice daily, according to clinical need.<sup>1</sup>

The mechanism of action of ranolazine is unknown, but it is thought to exert its effects by inhibiting late sodium currents in cardiac cells, thus reducing ionic imbalances during ischemia.<sup>1</sup> These changes occur independently of reductions in blood pressure and / or heart rate.<sup>1</sup>

### How effective is it?

The double-blind MARISA<sup>2</sup> and CARISA<sup>3</sup> phase III studies enrolled patients with coronary artery disease and exertional angina (for > three months).<sup>2,3</sup> The primary endpoint for both studies was total exercise treadmill test (ETT) duration at 12 hours post-dose (trough).<sup>2,3</sup> Secondary endpoints included the mean weekly number of angina attacks, amongst others.<sup>2,3</sup>

MARISA was a dose-finding study that randomised patients (n = 191) to receive placebo or MR ranolazine 500mg, 1000 mg or 1500 mg, twice daily for one week, with a crossover design.<sup>2</sup> ETT duration increased by 23.8, 33.7 and 45.9 seconds above placebo, respectively (p ≤ 0.003 for all).<sup>2</sup> Doses above 1000 mg twice daily should not be used in clinical practice due to a disproportionate increase in adverse drug reactions (ADRs).<sup>2</sup>

Ranolazine was investigated as an adjunctive anti-anginal therapy in the CARISA study.<sup>3</sup> Patients (n = 823) were stratified by their background therapy of atenolol (50 mg/day) or amlodipine (5 mg/day) or diltiazem (180 mg/day), and randomised to receive placebo, 750 mg or 1000 mg MR ranolazine, twice daily, for 12

weeks as add on therapy.<sup>3</sup> At 12 weeks, ETT duration above baseline was increased by 23.7 and 24.0 seconds for 750 and 1000 mg ranolazine, respectively, compared to placebo (p = 0.03 for both).<sup>3</sup> Ranolazine reduced the mean number of angina attacks per week in a dose-dependent manner, from 3.3 with placebo, to 2.5 and 2.1 for 750 and 1000 mg MR ranolazine respectively (p ≤ 0.006 for both).<sup>3</sup> A limitation of this study was that the background anti-anginal therapies were prescribed at starting doses, rather than fully optimised combination treatment at maximally tolerated doses.<sup>4</sup>

The phase III double-blind ERICA study (n = 565) involved adults with chronic stable angina (≥ three angina attacks per week, for > three months) despite maximised amlodipine treatment, and 45% of patients also taking long-acting nitrates.<sup>5</sup> Patients were randomised to receive six weeks treatment with placebo or MR ranolazine 1000 mg, twice daily, in conjunction with amlodipine 10 mg/day.<sup>5</sup> The primary endpoint was the mean number of angina attacks per week. At week six, the trimmed mean number (after removing outliers from the data) of weekly angina attacks was slightly lower with ranolazine than placebo [2.88 vs. 3.31 (p = 0.028, respectively)].<sup>5</sup> No significant differences were observed between the groups when a conventional mean was used. The long-term efficacy of ranolazine was not established and the dose used was higher than the current licensed maximum.

In the MERLIN-TIMI 36 randomised, double-blind trial (n = 6560) for patients with non-ST-elevation acute coronary syndromes, administration of ranolazine for a median of 348 days did not reduce major cardiovascular events, or adversely affect the risk of all-cause death or symptomatic arrhythmia, compared with placebo.<sup>6</sup> Discontinuation due to an adverse effect was reported significantly more frequently with ranolazine than with placebo [8.8% vs. 4.7%, (p < 0.001) respectively].<sup>6</sup>

There are no trials available investigating the efficacy of ranolazine in patients who are intolerant to first-line anti-anginal therapies.

## How safe is it?

The MARISA and CARISA studies showed dose-related ECG changes with administration of ranolazine,<sup>2,3</sup> including QTc interval prolongation of up to 9.2 milliseconds above placebo at a 1000 mg twice daily dose.<sup>2,3</sup>

In all three anginal studies, the rate of adverse drug reactions (ADRs) was higher in the groups administered ranolazine than placebo and increased in a dose-dependant manner. Overall, administration of 1000 mg MR ranolazine twice daily, resulted in a 5% average increase in the frequency of ADRs, compared with placebo.<sup>2,3,5</sup> The most common ADRs observed throughout the studies with ranolazine vs. placebo were: constipation (0 - 8.9% vs. 0 - 1.8%), dizziness (1.1 - 12.3% vs.  $\geq$  0.7 - 2.5%) and nausea (< 1 - 8.6% vs. 0 - 0.7%).<sup>2,3,5</sup>

Ranolazine is largely metabolised by the cytochrome P450 3A4 (CYP3A4) system, hence there is a potential for serious drug interactions. Due to this, it is contraindicated in combination with:

- Clarithromycin, grapefruit juice and other potent CYP3A4 inhibitors.<sup>1</sup>
- Class Ia and Class III anti-arrhythmics (other than amiodarone).<sup>1</sup>
- Patients with moderate to severe hepatic impairment and / or severe renal impairment.<sup>1</sup>

Caution is advised when prescribing ranolazine in combination with:

- Simvastatin and/or digoxin, as the plasma concentrations of simvastatin or digoxin may be increased.<sup>1</sup>
- Diltiazem, erythromycin and verapamil (and other moderate CYP3A4 and P-glycoprotein inhibitors).<sup>1</sup>
- Phenytoin, carbamazepine and St. Johns Wort (and other CYP3A4 inducers).<sup>1</sup>
- Pre-existing QTc prolongation or drugs causing this effect e.g. amitriptyline.<sup>1</sup>
- Some tri-cyclic anti-depressants and anti-psychotics (CYP2D6 inhibitors / substrates), as ranolazine is partially metabolised by CYP2D6, and also mildly inhibits this enzyme.<sup>1</sup>
- Patients with mild hepatic and / or mild to moderate renal impairment should have careful dose titration.<sup>1</sup>
- Elderly patients or those with low weight ( $\leq$  60 kg).<sup>1</sup>

## What other options are there?

Guidelines from the European Society of Cardiology, Scottish Intercollegiate Guidelines Network and Clinical Knowledge Summaries advise that initial treatment options for angina include managing lifestyle issues and ensuring co-morbidities are well controlled.<sup>7-9</sup> Acute attacks of stable angina should be managed with short acting nitrates.<sup>4,7-9</sup> Patients with mild to moderate stable angina should use beta-blockers as first-line therapy, however if monotherapy fails to control symptoms, combination treatment with a calcium-channel blocker or long-acting nitrate should be initiated, where appropriate.<sup>4,7-9</sup> Patients whose symptoms are not controlled with optimised / maximum therapeutic doses of two drugs, should be considered for referral to a cardiologist.<sup>4,7-9</sup> Anti-platelet therapy, lipid lowering therapy and ACE inhibitor therapy should be considered to reduce cardiovascular risk.<sup>4,7-9</sup> NICE is currently working on clinical guidelines for the management of stable angina, with publication due in 2011.<sup>10</sup>

## When should it be used?

Increases in ETT and reductions in angina attacks associated with the use of ranolazine are limited, and only one study has evaluated its addition to a combination of first-line anti-anginal treatments, as per guidelines; hence its clinical role remains uncertain. Concerns remain about ADRs, including the propensity for QT prolongation, drug interactions with a variety of medications used in patients with cardiovascular disease, and safety in liver and renal disease. Until further evidence of benefit and safety is available, prescribing of ranolazine should be initiated by cardiologists only. Ranolazine is not appropriate for treating patients with unstable angina.

## How much does it cost?

Ranolazine costs £1.63 per twice daily dose at 375, 500 or 750 mg.<sup>11</sup> The recommended starting dose is 375 mg MR ranolazine twice daily, titrated up to a maximum recommended dose of 750 mg twice daily,<sup>1</sup> therefore would cost £45.64 for 28 days treatment.

Administration of ranolazine should only be initiated in conjunction with first-line anti-anginal therapy. Anti-anginal therapy cost comparison charts are available at [www.nyrdtc.nhs.uk/Services/presc\\_supp/presc\\_supp.html](http://www.nyrdtc.nhs.uk/Services/presc_supp/presc_supp.html)

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KEY RCT - randomised controlled trial, G-guideline.

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