# PharmaNote®

VOLUME 21, ISSUE 9 JUNE 2006


## RANOLAZINE (RANEXA®): A NOVEL AGENT FOR ANGINA


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In the United States approximately 6.5 million people are affected by chronic angina.[1] Current anti-anginal medications work by reducing myocardial oxygen demand (β-blockers, calcium channel blockers, and nitrates) or improving oxygen supply (calcium channel blockers and nitrates). As many as 26% of patients continue to experience angina attacks despite medication and/or revascularization.[2] There is a clear need for additional, pharmacologic agents to address the treatment gap that exists in the management of angina.

Ranolazine (Ranexa®) is a new medication derived from piperazine for the treatment of severe chronic angina.[3] It is devoid of hemodynamic effects.[2,3,4] Ranolazine, marketed by CV Therapeutics, was approved by the FDA on January 31, 2006.[5] It is the first drug in a new class of medications, metabolic modulators.[6] This paper will discuss the pharmacology, pharmacokinetics, clinical trials, administration, precautions, and cost of ranolazine.

### Pharmacology and Pharmacokinetics

During an ischemic attack fatty acid levels rise, which promotes increased myocardial uptake and oxidation of fatty acids and reduced carbohydrate uptake. This imbalance of energy uptake leads to both oxygen wasting and lactate accumulation. Fatty acid oxidation is an inefficient use of oxygen. Carbohydrate (glucose, lactate, and pyruvate) oxidation is a more efficient use of oxygen since it provides 11% more adenosine triphosphate [ATP] per $O_2$ molecule.[3] Ranolazine appears to inhibit oxidation of fatty acids, forcing the myocardium to use the more efficient substrate, carbohydrates, for ATP production, especially in times of elevated fatty acid levels. This shift reduces the amount of oxygen that the cardiac muscle needs to function and aids in glycolysis and pyruvate oxidation coupling, reducing lactate accretion and resultant tissue necrosis.[4]

Ranolazine is administered orally twice a day and is available in 500 mg extended-release tablets. Peak plasma levels are seen in 2-5 hours with no change in area under the curve (AUC) and maximum plasma concentration (Cmax) when administered with or without food. Ranolazine is approximately 62% protein bound. Metabolism is primarily by CYP3A and CYP2D6. Ranolazine is also a P-glycoprotein substrate, making it susceptible to drug interactions. Ranolazine is contraindicated with moderate or potent CYP3A inhibitors. The half-life of the extended-

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**Table 1. Mean exercise treadmill test (ETT) in the MARISA trial.[4]**

| | Placebo (seconds) | | Ranolazine dose 500mg BID* | | 1000mg BID* | | 1500mg BID* | |
|---|---|---|---|---|---|---|---|---|
| | Trough | Peak | Trough | Peak | Trough | Peak | Trough | Peak |
| Exercise duration (s)** | 505.7 | 501.7 | 23.8 (4.7) | 29.3 (5.8) | 33.7 (6.7) | 50.1 (10.0) | 45.9 (9.1) | 55.5 (11.1) |
| Time to angina (s)** | 407.3 | 416.3 | 27.0 (6.6) | 35.5 (8.5) | 45.9 (11.3) | 56.4 (13.5) | 59.6 (14.6) | 68.5 (16.5) |
| Time to 1mm ST-segment depression (s)** | 443.4 | 436.4 | 27.6 (6.2) | 38.8 (8.9) | 44.5 (10.0) | 55.6 (12.7) | 64.6 (14.6) | 69.0 (15.8) |

* BID = twice a day. ** All results represent increases over placebo and showed statistical significance with $p \leq 0.005$.

release tablets is about seven hours, whereas its metabolites display longer half-lives, though it is unknown if they have pharmacological activity. Elimination is 75% renal and 25% fecal with <5% excreted unchanged by either route. [7]

## Clinical Trials

To date there have been several clinical trials involving ranolazine alone or in combination with other anti-anginal medications. The Monotherapy Assessment of Ranolazine In Stable Angina (MARISA), Combination Assessment of Ranolazine In Stable Angina (CARISA), and Efficacy of Ranolazine In Chronic Angina (ERICA) serve as the basis for FDA approval and are reviewed below.

The MARISA trial[4] evaluated ranolazine in 191 patients with angina-limited exercise. The study was a randomized, double-blind, four-period, crossover study comparing ranolazine extended-release 500 mg, 1000 mg, 1500 mg, and placebo all administered twice a day for one week. Patients were evaluated using exercise treadmill tests (ETT). All doses of ranolazine resulted in improved exercise tolerance, time to angina, and time to 1mm ST-segment depression (Table 1). Hemodynamic changes at rest and at maximal exercise where minimal and dose-related QTc interval increases were 6 ms, 7 ms, and 11 ms at trough and 5 ms, 6 ms, and 14 ms at peak for ranolazine doses of 500 mg, 1000 mg, and 1500 mg twice daily, respectively.

The CARISA trial[2] followed 823 patients for 12 weeks. Placebo, 750 mg, or 1000 mg of ranolazine all administered twice daily were added to existing background anti-anginal therapy. The study was a randomized, double-blind, three-group study that enrolled patients receiving anti-anginal medication to evaluate if ranolazine could improve patients' exercise tolerance. At baseline, 44.6% of the patients were on atenolol, 29.8% on amlodipine, and 25.6% on diltiazem. The results are shown in Table 2. No clinically significant hemodynamic changes were reported and dose related QTc interval changes were 6.1 ms for ranolazine 750 mg twice daily and 9.2 ms for 1000 mg twice daily.

The ERICA trial[8] has yet to be published, though the abstract is available. The trial enrolled 565 patients being treated with amlodipine 10 mg. Patients were treated with ranolazine 500 mg twice a day and titrated to 1000 mg twice daily or placebo and followed for six weeks in a double-blind fashion. Ranolazine provided incremental benefit (see Table 3.) in patients with angina. These results appear to be consistent across age, gender, and background nitrate subgroups.

## Dosing and Administration

Ranolazine is available as 500 mg extended-release oral tablets and is indicated for the treatment of chronic angina. Due to risks of QTc prolongation it should be reserved for patients that have had an inadequate response to other treatment modalities. Treatment with ranolazine should be initiated at 500 mg twice daily and titrated to 1000 mg twice a day if the initial response is suboptimal. The maximum daily dose is 1000 mg twice daily. If a dose is missed, it should be skipped and the next dose taken as scheduled.[7]

The dose of ranolazine should be reduced in patients with mild to severe renal or hepatic impairment.[9,10] Blood pressure and ECG monitoring is indicated due to the potential for QTc prolongation. No dosing adjustments are required according to age or gender or in patients with diabetes mellitus or congestive heart failure (CHF) NYHA Class I to IV.

**Table 2. Mean ETT results for ranolazine and placebo in the CARISA trial.[2]**

| | Increase versus placebo | | | |
|---|---|---|---|---|
| **Ranolazine Dose** | **750 mg BID*** | | **1000 mg BID*** | |
| | Trough | Peak | Trough | Peak |
| Exercise duration (s) | 23.7** | 34.0** | 24.0** | 26.1** |
| Time to angina (s) | 29.7** | 38.0** | 26.0** | 37.9** |
| Time to ECG ischemia (s) | 19.9 | 40.8** | 21.1 | 34.5** |

* BID = twice a day. ** Results showed statistical significance with $p \leq 0.03$.

Studies have not assessed whether dosing adjustments are needed according to hemodialysis, race or in pediatric patients.[7]

## Contraindications

Ranolazine is contraindicated in patients with pre-existing or history of QT prolongation or concomitant use of drugs that prolong the QT interval, hepatic impairment, ventricular arrhythmias, or use of potent CYP3A inhibitors. It should be used with caution in patients with cardiac arrhythmias or renal impairment.[7]

Ranolazine is pregnancy category C and it is unknown whether ranolazine, or its metabolites, are excreted into breast milk.[7]

## Toxicity and Safety

Ranolazine's adverse event profile is dose-related. The most frequently reported adverse drug events at 500 mg and 1000 mg twice a day are dizziness (1.1%, 5%), asthenia (0%, 1.7%), constipation (0%, 1.7%), angina pectoris (5%, 1.7%), nausea (<1%, 1.1%), and headache (<1%, 1.1%).[4] No cases of overdose have been reported but ECG monitoring and supportive care should be initiated in such cases due to concentration dependent QTc prolongation.[7]

## Drug Interactions

Drug interactions with ranolazine result from inhibition of CYP3A by other medications including the potent inhibitor ketoconazole and moderately potent inhibitor diltiazem. Less potent inhibitors and substrates such as simvastatin and cimetidine do not appear to affect the plasma concentration. Verapamil, a CYP3A and P-glycoprotein inhibitor, increases plasma concentrations significantly. Consequently when administering ranolazine care should be used with concurrent use of CYP3A and/or P-glycoprotein inhibitors as plasma concentrations may increase 1.8- to 3.2-fold. The potent CYP2D6 inhibitor paroxetine, at 20 mg daily increased ranolazine plasma concentrations 1.2-fold. The manufacturer does not recommend dosage adjustments in cases of concomitant CYP2D6 inhibitor use. Digoxin does not affect ranolazine concentrations.[7,11]

*In vitro* studies indicate that ranolazine and its O-demethylated metabolite are inhibitors of CYP3A and CYP2D6. Ranolazine does not inhibit CYP1A2, 2C9, 2C19, and 2E1. Ranolazine increases serum levels of simvastatin, a CYP3A substrate, by 2-fold. Diltiazem is unaffected by ranolazine. CYP2D6 is inhibited to a lesser degree however medications that are 2D6 substrates may require reduced doses. Digoxin levels are increased 1.5-fold when used in conjunction with ranolazine.[7,11]

**Table 3. Mean number of angina attacks and nitroglycerin* use per week in ERICA trial.[8]**

| | Baseline | Placebo | Ranolazine 1000mg BID | P value of Ranolazine vs. placebo |
|---|---|---|---|---|
| Number of angina attacks | 5.6 | 3.2 | 2.8 | 0.028 |
| Number of NTG use | 4.6 | 2.6 | 2.0 | 0.014 |

* Tablets or sprays

## Cost

Ranexa® 500 mg extended-release tablets are available in 60 count unit-of-use bottles and 500 count pharmacy stock bottles.[7] According to a pharmaceutical distributor, the average wholesale price (AWP) of one month supply is $206.25. The average retail price for a one month supply in Gainesville, Florida is $214.99.

## Summary

Ranolazine (Ranexa®) is a novel drug for the treatment of chronic angina.[1] It works through metabolic modulation by decreasing fatty acid metabolism in ischemic cardiac tissue with a concomitant increase in carbohydrate utilization resulting in more efficient energy synthesis.[4] It is effective as monotherapy;[4] however, it will likely have the greatest impact when added to conventional therapy with agents such as atenolol, diltiazem, or amlodipine.[2]

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### New Drug Approvals

Insulin detemir, a long-acting insulin, is now available as Levemir® (Novo Nordisk) in 10 ml vials and a 3 ml FlexPen (100 Units/ml) for the treatment Type 1 diabetes mellitus (adults and children) and Type 2 diabetes mellitus (adults) when basal insulin is indicated.


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**The Department of Pharmacy Services, UF Family Practice Medical Group, Departments of Community Health and Family Medicine and Pharmacy Practice**