National PBM Drug Monograph
Ranolazine (Ranexa®)
June 2007
VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

EXECUTIVE SUMMARY

Ranolazine was approved by the FDA in January 2006. Ranolazine differs from traditional anti-anginal agents (beta-blockers, calcium channel blockers and long-acting nitrates) in that its anti-anginal and anti-ischemic effects are independent of reductions in blood pressure and/or heart rate. Although the exact mechanism of action is not known, ranolazine is believed to reduce angina/ischemia by selectively inhibiting the late sodium current resulting in reduced intracellular sodium and calcium overload during ischemia.

Efficacy

- Ranolazine's effectiveness as an anti-anginal drug has been examined in three randomized, double-blind, placebo-controlled clinical trials involving nearly 1600 patients. In two of the three studies, the primary endpoint (treadmill exercise duration) was increased by about 24 seconds more than placebo (ranolazine trough concentration). At peak concentrations, exercise duration, time to angina and time to 1 mm ST-segment depression was approximately 30-55 seconds longer in the ranolazine vs. placebo group. (In one study, ranolazine was used as monotherapy. In the second study, it was added to submaximal doses of amlodipine, atenolol or diltiazem.)
- In two of the three clinical trials, evaluating the anti-anginal effect of ranolazine, mean weekly angina episodes and mean weekly consumption of SL NTG was assessed. The difference between ranolazine and placebo was about 0.3-0.6 less episodes of angina and 0-1 less SL NTG consumed per week in favor of ranolazine. However, baseline weekly angina and SL NTG consumption were 0.4-0.6 (episodes or tablets) higher in the placebo group.
- The effect of ranolazine was not consistently improved with escalation in dose.
- In a subgroup analysis of the ERICA trial, patients with more than 4.5 episodes of angina per week were responsible for the statistical difference from placebo.
- In a fourth study, the addition of ranolazine or placebo to standard therapy in 6,560 patients presenting with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) was examined. The primary outcome measure was an effect on a composite outcome of CV death, MI or recurrent ischemia. There was no difference between ranolazine and placebo.
- Quality of life was measured using the Seattle Angina Questionnaire (SAQ) (see page 6 for definition). Angina frequency was measured in two studies and improved by approximately 2-4 points more with ranolazine vs. placebo (scale of 0-100).
- Anti-anginal effect appeared to be less in women than in men in at least two of the trials.

Safety

- In all four clinical trials involving the sustained-release dosage form of ranolazine, adverse events were higher in the ranolazine groups vs. placebo. Additionally, the rate of withdrawal due to adverse events was higher in at least two of the studies.
- The most common adverse events were constipation, nausea, dizziness, headache and asthenia.
- Adverse events increased with escalation in dose.
- In all of the 64 clinical trials, involving both the ranolazine immediate and sustained release dosage forms in the integrated safety summary (ISS) database, 19.2% of patients on ranolazine reported syncope, symptoms suggestive of syncope or presyncope vs. patients on placebo (4.4%).
- Syncope was reported more often in the ranolazine group in two of the four clinical trials using the FDA approved dosage form.
- Ranolazine is known to increase the QT interval, has many drug-drug interactions and multiple precautions for its use. As a result, the FDA has recommended that it be used in those patients having an inadequate response with other anti-anginal drugs.

FDA Approved Indication

- Ranolazine is approved for the treatment of chronic angina. Because ranolazine prolongs the QT interval, it should be reserved for patients who have not received an adequate response with other antianginal drugs.
- It should be used in combination with beta-blockers, nitrates or dihydropyridine (e.g. felodipine, amlodipine or long-acting forms of nifedipine) calcium channel blockers.

Dosage and Administration

- The initial dose of ranolazine is 500 mg twice daily. The dose can be increased to 1000 mg twice daily, if needed, based upon clinical symptoms. (However, increased doses have not consistently been shown in clinical trials to improve symptoms compared to the starting dose. Adverse events are dose-related).
- The maximum dose is 1000 mg twice daily.
- Baseline and follow-up electrocardiograms (ECG) should be obtained to examine the effect of ranolazine on the QT interval.
- Dose adjustment of object drug, avoidance of ranolazine or avoidance of certain drug combinations with ranolazine is recommended in specific circumstances (e.g. drug-drug interactions, special populations).
- Ranolazine can increase simvastatin concentrations 2-fold, reduce simvastatin dose upon initiation of ranolazine.
- Ranolazine may be taken without regard to meals. The tablets should be swallowed whole and NOT be broken, crushed or chewed.

Precautions

- **Effect on QTc Interval**
- Ranolazine has been shown to prolong the QT interval in a dose-dependent manner. The mean increase in QTc, associated with the 1000 mg twice daily dose of ranolazine (trough concentrations), is approximately 6 milliseconds (ms). In 5% of the population studied, the QTc was prolonged 15 ms.
- **Renal Impairment**
- In a small group of patients with severe renal impairment (Creatinine Clearance <30 ml/min and not receiving dialysis), diastolic blood pressure was increased approximately 15 mm Hg with repeat dosing of ranolazine. As a result, blood pressure should be regularly monitored in these patients.
- **Laboratory Tests**
- Increases in serum creatinine were observed in subjects receiving ranolazine (mean 0.1 mg/dl) and were reversible upon discontinuation. Changes in BUN were not observed.
- Temporary eosinophilia was infrequently noted with ranolazine. During clinical trials, small reductions in hematocrit (mean 1.2%) were observed in patients on ranolazine, with no evidence of occult blood loss.
- **Drug-Drug Interactions**
- Refer to drug-drug interaction section on pages 11 and 12 of this monograph. There are numerous drug-drug interactions to consider when prescribing ranolazine.

Contraindications

Since ranolazine has been observed to prolong the QT interval in a dose-dependent manner, its use is contraindicated in the following individuals because of the potential for a greater prolongation of the QT interval:

- Patients with pre-existing QT prolongation
- Patients with mild, moderate or severe hepatic impairment [Child-Pugh Classes A (mild), B (moderate) or C (severe)].
- Patients on QT prolonging drugs (e.g. Class Ia [quinidine] or Class III [amiodarone, dofetilide, sotalol] antiarrhythmics, erythromycin and some antipsychotic agents [thioridazine, ziprasidone]) (list is not comprehensive).[8-9]

- Patients receiving potent or moderately potent CYP 3A4 inhibiting drugs, including azole antifungals, amiodarone, macrolide antibiotics, HIV protease inhibitors, grapefruit juice, diltiazem and verapamil (list is not comprehensive).[22]

Place in Therapy

Because ranolazine is capable of prolonging the QT interval, has multiple drug-drug interactions and precautions for its use, it can be considered for use in those patients with chronic stable angina, having no contraindications, with an inadequate response to therapeutic doses of beta-blockers, long-acting dihydropyridine CCBs and long-acting nitrates. Additionally, patients who are not considered candidates for revascularization (PCI or CABG), are receiving maximal anti-anginal therapy and possessing no contraindications may consider use of ranolazine for their symptoms. Patients should be closely monitored for an improvement in anginal symptoms. If the patient does not feel ranolazine has improved their symptoms, it should be discontinued.

INTRODUCTION

Ranolazine is an anti-anginal drug approved by the US FDA in January 2006. The purpose of this monograph is to (1) evaluate the available evidence of safety, tolerability, efficacy, cost and other pharmaceutical issues that would be relevant to evaluating ranolazine for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in VHA.

PHARMACOLOGY/PHARMACOKINETICS[1-2]

Ranolazine differs from traditional anti-anginal agents in that its anti-anginal and anti-ischemic effects are independent of reductions in blood pressure and/or heart rate. Although the exact mechanism of action is not known, ranolazine is believed to reduce angina/ischemia by selectively inhibiting the late sodium current resulting in reduced intracellular sodium and calcium overload during ischemia. This effect of ranolazine may favorably alter cardiac metabolic pathways through partial inhibition of fatty acid oxidation. During periods of myocardial ischemia, increases in fatty acid metabolism occur which can be detrimental to the heart. By partially inhibiting β-oxidation of fatty acids, fatty acid oxidation is reduced and glucose oxidation is increased. This change in metabolism is more energy efficient since glucose oxidation generates more adenosine triphosphate (ATP) per oxygen molecule consumed thereby creating a reduced demand for myocardial oxygen. Ranolazine can also inhibit other ion currents including late I_{cal}, late I_{Na} and I_K.

Table 1. Pharmacokinetics

Parameter	Ranolazine
Metabolism	Extensively metabolized in the liver and intestine. (Primarily by CYP 3A4 and to a lesser extent 2D6).
Active Metabolites	Yes, 4 most abundant metabolites have activity 5-33% that of the parent compound
Absorption/distribution	Absorption is highly variable (95% Cmax values ranged 420-6080 ng/mL)
Elimination	75% of dose excreted in urine, 25% in feces (<5% excreted unchanged in urine or feces).
Half-life	Terminal half-life is 7 hours
Steady State Achieved	Within 3 days with twice daily dosing of ER tablets
Protein Binding	62%
Bioavailability	76%
Effect of Food on Cmax and AUC	No clinically significant effect

*****AUC=area under the concentration-time curve, Cmax=peak concentration achieved with regular dosing,

Ranolazine is both a substrate for and an inhibitor of cytochrome (CYP) 3A4 and to a lesser extent 2D6. It is also a substrate for and inhibitor of P-glycoprotein (P-gp). With repeated dosing, the AUC and Cmax of ranolazine increase slightly more than in proportion to dose (e.g. 500 mg increased to 1000 mg twice daily increases Cmax and AUC 2.2 and 2.4 fold, respectively).

Special populations

a. Age, gender or race

A pharmacokinetic evaluation of the effect of age and gender on ranolazine pharmacokinetics did not demonstrate differences. As a result, no dose modification is recommended.

The majority of subjects in the ranolazine clinical studies were Caucasian and so the effect of race on ranolazine pharmacokinetics has not been evaluated. Additionally, about 75% of subjects in phase 2/3 clinical trials were men. In two studies measuring exercise duration, the effect of ranolazine in women was less than that observed in men. However, in another study examining average weekly frequency of angina and sublingual nitroglycerin (SL NTG) consumption, there was no gender differences.

b. Renal insufficiency[1,3]

In a small pharmacokinetic study involving 29 patients with varying degrees of renal impairment (n=7 mild, 7, moderate, 7 severe renally impaired, 8 normal renal function), ranolazine's area under the concentration time curve (AUC_{0-12}) was significantly increased in patients with any degree of renal impairment (mild 1.72, moderate 1.89, severe 1.97) compared to healthy subjects. In those patients with severe renal impairment, mean diastolic blood pressure increased from 12 to 17.4 mm Hg by the third day of dosing and resolved upon cessation of dosing. The effect of dialysis on ranolazine pharmacokinetics has not been evaluated.

c. Hepatic insufficiency[1,4]

In a small pharmacokinetic study, investigators set out to determine the effect of mild (Child-Pugh Grade A) and moderate (Child-Pugh Grade B) hepatic impairment on the pharmacokinetics of ranolazine compared to subjects with normal liver function. A total of 32 patients were enrolled (n=8 mild, 8 moderate and 16 normal hepatic function). Moderate hepatic impairment was associated with a 76% increase in AUC_{0-12}, 51% increase in C_{max}, and more than a doubling of C_{trough} compared to healthy subjects. Ranolazine plasma concentrations were also increased (1.3 fold) in patients with Child-Pugh Class A hepatic impairment.

The manufacturer's labeling states that patients with mild to moderate liver impairment were observed to have increases in their QTc intervals that were larger than that observed in healthy individuals at similar plasma ranolazine concentrations.

d. Congestive heart failure/Diabetes mellitus[1]

Population pharmacokinetic studies did not show an effect of NYHA Class I-IV or diabetes mellitus on the pharmacokinetics of ranolazine.

FDA APPROVED INDICATION(S) AND Off-LABEL USES[1]

Ranolazine is approved for the treatment of chronic angina. Because ranolazine prolongs the QT interval, it should be reserved for patients who have not received an adequate response with other antianginal drugs. It should be used in combination with beta-blockers, nitrates or dihydropyridine (e.g. felodipine, amlodipine or long-acting forms of nifedipine) calcium channel blockers.

CURRENT VA NATIONAL FORMULARY ALTERNATIVES

Beta-Blockers

atenolol
metoprolol (long and short acting dosage forms)
propranolol (long-acting formulations)
carvedilol (restricted to criteria)

Calcium Channel Blockers

Nondihydropyridine:

diltiazem (long and short acting dosage forms)
verapamil (long and short acting dosage forms)

Dihydropyridine:
amlodipine
felodipine
nifedipine (long-acting dosage forms)

Short and Long-acting Nitrates
isosorbide dinitrate
isosorbide mononitrate
nitroglycerin patch

DOSAGE AND ADMINISTRATION

The initial dose of ranolazine is 500 mg twice daily. The dose can be increased to 1000 mg twice daily, if needed, based upon clinical symptoms. (However, increased doses have not consistently been shown in clinical trials to improve symptoms compared to the starting dose. Adverse events are dose-related). The maximum dose is 1000 mg twice daily. Baseline and follow-up electrocardiograms (ECG) should be obtained to examine the effect of ranolazine on the QT interval.

Because ranolazine has been observed to increase simvastatin concentrations 2-fold, the dose of simvastatin may need to reduced when combined with ranolazine.

When administering ranolazine in combination with substrates for P-gp (e.g. digoxin), the dose of those agents may need to be reduced since *in vitro* studies indicate that ranolazine is an inhibitor of P-gp. Additionally, *in vitro* studies indicate that ranolazine is a substrate for P-gp and caution should be used when administered known inhibitors of P-gp with ranolazine (e.g. ritonavir, cyclosporine, etc.).

Ranolazine may be taken without regard to meals. The tablets should be swallowed whole and NOT be broken, crushed or chewed.

EFFICACY

There are two primary goals when considering drug therapy for patients with chronic angina. First, treatment should begin with vasculoprotective agents, those agents proven to reduce cardiovascular events (e.g. myocardial infarction [MI] or death), such as aspirin and lipid-lowering therapy (statins). Second, initiation of anti-ischemic or anti-anginal drug therapy helps to reduce or eliminate anginal symptoms and improve quality of life. This section will focus on those agents that reduce ischemia and angina symptoms.[10-11]

Traditional drug treatment for symptomatic chronic angina involves the use of beta-blocking and/or calcium blocking agents as well as short and long-acting nitrates. Beta-blockers decrease oxygen demand by reducing heart rate, blood pressure and myocardial contractility. Because beta-blockers have been demonstrated to decrease mortality after an MI, they are generally recommended as first-line therapy in the majority of patients.[10] Dosing should be adjusted, while monitoring symptoms, to a heart rate of 55-60 beats per minute (bpm).

Calcium channel blocking (CCB) agents can be separated into two categories, dihydropyridine and nondihydropypridine calcium channel blockers. Calcium channel blockers decrease oxygen demand by dilating coronary arteries, reducing blood pressure and improving myocardial blood flow. The nondihydropyridine CCBs (diltiazem and verapamil) also reduce anginal symptoms by decreasing heart rate and myocardial contractility. Short-acting dihydropyridine CCBs should not be used to treat angina since they have been found to increase the risk for adverse cardiac events. However, slow-release or long-acting dihydropyridine and nondihydropyridine CCBs are effective antianginal agents and do not increase the risk for adverse cardiac events.

Short and long-acting nitrates reduce oxygen demand by reducing preload and also increasing blood supply to the epicardial coronary arteries. Nitrates are effective anti-anginal drugs; however, continuous administration can rapidly lead to the development of nitrate tolerance. By providing a 10-14 hour nitrate free interval, nitrate tolerance can be avoided. The limitation of using nitrates as single therapy for angina is

that the 10-14 hour nitrate free interval essentially leaves the patient without anginal protection during this period. As a result, nitrates are typically used as add-on therapy to beta-blockers or CCBs.
In a meta-analysis of clinical trials comparing beta-blockers, CCBs, and nitrates for chronic angina, both beta-blockers and CCBs provided similar clinical outcomes with beta-blockers having a slight advantage in terms of reduced weekly angina episodes and fewer adverse events. There were an inadequate number of trials directly comparing nitrates with beta-blockers or CCBs to determine equivalent effectiveness.[12]

Ranolazine is the first antianginal to be approved by the FDA in more than 20 years. It is unique from the traditional drug therapies in that its anti-ischemic effect appears to be mostly independent of a hemodynamic effect.

In many cases, medical treatment of anginal symptoms may involve the use of 2 or more agents. The dose of each drug should be adjusted to achieve maximum benefit and safety. In a study of more than 7,000 veterans with angina, only 70% were believed to be adequately treated with medications.[13] Of the 30% that were not adequately treated, 55% either received none or only one anti-anginal drug and 21% were not receiving an adequate dose. Combination drug therapy for angina typically includes a beta-blocker or CCB with a long-acting nitrate. If beta-blockers and CCBs are combined, dihydropyridine CCBs are preferred.

Efficacy Measures
All traditional anti-anginal agents (e.g. beta-blockers, CCBs, nitrates) have been shown to prolong exercise duration, time to ST-segment depression and reduce the frequency of angina. However, none to date have been shown to reduce clinically important outcomes such as MI or death in patients being treated specifically for chronic stable angina. As stated above, clinical trials comparing the older available therapies have not shown a significant advantage of one agent over the other. So, selection should be based upon patient characteristics with a preference for initiation of a beta-blocking agent if no contraindications exist. The following efficacy measures were used in the clinical trials involving ranolazine:

- Exercise treadmill testing (ETT): A noninvasive diagnostic tool used in patients with known or suspected ischemic heart disease. Modified Bruce Protocol ETT: This test begins with a lower workload than the Bruce protocol and is generally used in those patients who are post myocardial infarction, those whose history suggests ischemia at reduced workloads and in elderly or sedentary patients who are unable to keep up with the faster pace of the Bruce protocol. The test is positive if typical chest pain occurs or diagnostic ST segment depression occurs during the test.

- Average number of weekly anginal episodes and/or average weekly consumption of sublingual (sl) nitroglycerin (NTG) tablets. These endpoints are self-reported and kept in a diary by patients.

- Seattle Angina Questionnaire (SAQ): The SAQ is a 19 item questionnaire intended to measure functional status in patients with CAD. The questionnaire is composed of 5 scales to assess important dimensions of CAD (physical limitation, anginal stability, anginal frequency, treatment satisfaction and disease perception). Each dimension is scored on a scale of 0-100. For each dimension, the higher the score, the less problematic the angina is for the individual. The SAQ has been validated to be responsive to major changes in clinical status and smaller changes in angina functional status. It is used to assess quality of life in two ranolazine studies.

- Reduction in cardiovascular (CV) outcomes such as CV death, MI, or recurrent ischemia

Summary of Efficacy Findings
Only those trials evaluating the efficacy and safety of the long-acting (FDA approved) dosage form of ranolazine are included. (For additional details regarding the clinical trials, see appendix A)

To date, there have been four clinical trials[14-15, 17,19] evaluating the efficacy and safety of ranolazine (sustained release). In three of the four studies, patients with chronic stable angina were randomized to receive ranolazine or placebo for a period of 4-12 weeks to determine if ranolazine was more effective than placebo in reducing angina/myocardial ischemia.[14-15,17] In the fourth study, the addition of ranolazine or placebo to standard therapy for non-ST-segment elevation acute coronary syndrome (NSTE-ACS) was

examined to determine the incremental reduction in a composite of CV events (e.g. CV death, MI or recurrent ischemia).[19] All four studies were randomized, double-blind, multi-center and placebo-controlled. The inclusion criteria were similar for the 3 angina endpoint studies which enrolled patients 18 years and older with known CAD and at least a 3 month history of angina. The exclusion criteria were generally similar in all four studies and included conditions that may alter the ability to interpret the electrocardiogram (ECG) (e.g. digoxin, left bundle branch block, ≥ 1 mm ST-segment depression at rest, pacemaker, etc.); NYHA Class III or IV CHF; receiving medications known to prolong the QT interval; receiving drugs inhibiting CYP 3A4 metabolism, etc. (see appendix A for specific exclusion criteria for each study).

In two of the three angina endpoint studies,[15,17] investigators evaluated the addition of ranolazine to traditional anti-anginal drug treatments (e.g. atenolol, diltiazem or amlodipine). The third study was a dose-ranging, cross-over study in which patients were given 3 different doses of ranolazine and placebo each at one-week intervals.[14] In two studies[14-15], efficacy evaluations were conducted at 4 and 12 hours (peak and trough concentrations, respectively) after dosing to ensure the 12 hr dosing interval was adequate.

At trough ranolazine concentrations, exercise duration was increased by about 24 seconds with ranolazine versus placebo. At peak concentrations, exercise duration, time to angina and time to 1 mm ST-segment depression was increased by approximately 30-55 seconds in the ranolazine groups compared to placebo.

In ERICA, the average reduction in weekly episodes of angina was 2.71 for ranolazine and 2.37 for placebo (difference 0.34, p=0.028). In CARISA, mean weekly angina episodes was reduced 1.3 for placebo and 1.9 for ranolazine (difference 0.6). However, baseline averages were 0.6 higher in the placebo group. In ERICA and CARISA, average weekly consumption of SL NTG consumption was reduced 2.34 for placebo and 2.4 for ranolazine (baseline average was 0.6 SL NTG higher for placebo) and 0.97 for placebo and 1.9 for ranolazine (baseline average was 0.4 higher for placebo), respectively. In ERICA, patients with more than 4.5 episodes of angina per week were responsible for the statistical differences. In ERICA and MERLIN-TIMI 36, angina frequency was reduced with ranolazine vs. placebo but not physical limitation.

An analysis of the CARISA trial was done to determine if there were differences in efficacy assessments between diabetics and non diabetics. In that analysis, the anti-anginal effectiveness of ranolazine was similar in those with or without diabetes. A *post hoc* analysis of that subgroup analysis showed a significant reduction in hemoglobin A1C (HGB A1C) in those receiving ranolazine 750 mg and 1000 mg vs. placebo (0.48 and 0.7, respectively vs. placebo, p=0.0002).[20] This effect of ranolazine will be investigated further.[18]

Although the majority of subjects enrolled in clinical trials were male (approx. 75%), subgroup analysis of MARISA and CARISA showed a reduced benefit of ranolazine in women vs. men. In both trials, exercise treadmill testing was the instrument used to measure effectiveness of treatment. In ERICA, there was no difference in average weekly episodes of angina, sublingual nitroglycerin consumption or quality of life as assessed using the SAQ scores between men and women. One group of authors has published a discussion of these gender differences and concluded that the differences between exercise testing and angina frequency are unclear but may include differences in demographics, reasons for stopping exercise and type of exercise used.[21]

Table 2. Summary of Clinical Trials Involving Ranolazine

	MARISA[14]	**CARISA[15]**	**ERICA[17]**	**MERLIN-TIMI 36[19]**
Population	Chronic stable angina ≥ 3 months	Chronic stable angina ≥ 3 months and positive modified Bruce ETT on fixed-dose, background anti-anginals. (atenolol 50, amlodipine 5, diltiazem SR once daily)	Chronic stable angina ≥ 3 months and ≥ 3 angina episodes/week during 2 week qualifying phase on amlodipine 10 mg once daily	Hospitalization with NSTE-ACS within 48 hrs of ischemic symptoms and at least one indicator of moderate to high risk of death or recurrent ischemic events

N	191	823	565	6560
Intervention	Ran 500, 1000, 1500 mg, Pla twice daily	Ran 750, 1000 mg, or Pla twice daily and fixed doses of atenolol, amlodipine or diltiazem SR	Ran 500x1 week, 1000 mg or Pla twice daily added to amlodipine 10 mg	Ran IV 21-96 hrs followed by 1000 mg Ran or Pla twice daily for a minimum of 6 months. Doses could be reduced for ADEs
Study Duration	4-one week intervals (cross-over study)	12 weeks	6 weeks	Median 348 days (minimum 6 months)
Measure of Efficacy	Modified Bruce ETT	Modified Bruce ETT	Self-reported, weekly episodes of angina and weekly consumption of SL NTG, SAQ	CV outcomes, 7-day post-NSTE-ACS holter monitoring, angina frequency and physical limitation dimensions of SAQ
Primary Endpoint	Total exercise duration at Ran trough conc.	Effect on treadmill exercise duration at Ran trough conc.	Self-reported average weekly episodes of angina/	Composite CV events: CV death, MI, recurrent ischemia
Major Secondary Endpoint	Total exercise duration, time to angina, time to ST-segment depression of $\geq$ 1 mm at peak and trough Ran conc.	Total exercise duration, time to angina, time to ST-segment depression of $\geq$ 1 mm at peak and trough Ran conc.	Self-reported average weekly consumption of SL NTG and SAQ	Composite CV events: CV death, MI, severe recurrent ischemia; failure of treatment, QOL using physical limitation and angina frequency dimensions of SAQ, assessment of first 30 days (CV death, MI or recurrent severe ischemia or positive holter for ischemia)
Results-Primary Endpoint	Mean difference from Pla: Total exercise duration: **Trough:** Ran 500: 23.8 sec. (p=0.003) Ran 1000: 33.7 sec. (p<0.001) Ran 1500: 45.9 sec. (p<0.001)	Mean difference from Pla: Total exercise duration: **Trough:** Ran 750: 23.7 sec. (p=0.03) Ran 1000: 24 sec. (p=0.03)	Self-reported mean angina episodes: **Baseline:** Pla: 5.68 Ran: 5.59 **On treatment:** Pla: 3.31 Ran: 2.88 (p=0.028)	Composite CV death, MI or recurrent ischemia: Pla: 753 (23.5%) Ran: 696 (21.8%) HR=0.92, 95% CI 0.83-1.02, p=0.11
Results-Secondary Endpoint	Mean difference from Pla: Total exercise duration: **Peak:** Ran 500: 29.3 sec. (p<0.001) Ran 1000: 50.1 sec. (p<0.001) Ran 1500: 55.5 sec. (p<0.001) Time to angina: **Trough:** Ran 500: 27 sec, (p=0.005) Ran 1000: 45.9 sec. (p<0.001) Ran 1500: 59.6 sec. (p<0.001) **Peak:** Ran 500: 35.5 sec. (p<0.001) Ran 1000: 56.4 sec. (p<0.001) Ran 1500: 68.5 sec.	Mean difference from Pla: Total exercise duration: **Peak:** Ran 750: 34 sec. (p=0.001) Ran 1000: 26.1 sec. (p=0.02) Time to angina: **Trough:** Ran 750: 29.7 sec. p=0.01) Ran 1000: 26 sec. (p=0.03) **Peak:** Ran 750: 38 sec. (p=0.002) Ran 1000: 37.9 sec.(p=0.003) Time to ST-segment depression: **Trough:**	Self-reported mean SL NTG consumption: **Baseline:** Pla: 5.02 Ran: 4.43 (p=0.18) **On treatment:** Pla: 2.68 Ran: 2.03 (p=0.014) SAQ: Angina frequency was the only dimension that improved on Ran vs. Pla (22.5 vs. 18.5, respectively, p=0.008)	Composite CV death, MI or severe recurrent ischemia: Pla: 625 (19.2%) Ran: 602 (18.7%) HR=0.96, 95% CI 0.86-1.08, p=0.5 CV Death: Pla: 148 (4.5) Ran: 147 (4.4) HR 1, 95% CI 0.79-1.25, p=0.98 MI: Pla: 242 (7.6%) Ran: 235 (7.4%) HR 0.97, 95% CI 0.81-1.16), p=0.76 Recurrent ischemia: No difference in ischemia on ECG, hospitalization for ischemia or revasc.

	(p<0.001) Time to ST-segment depression **Trough:** Ran 500: 27.6 sec. (p<0.001) Ran 1000: 44.5 sec. (p<0.001) Ran 1500: 64.6 sec. (p<0.001) **Peak:** Ran 500: 38.8 sec. (p<0.001) Ran 1000: 55.6 sec. (p<0.001) Ran 1500: 69 sec. (p<0.001)	Ran 750: 19.9 sec. (p=0.1) Ran 1000: 21.1 sec. (p=0.09) **Peak:** Ran 750: 40.8 sec. (p<0.001) Ran 1000: 34.5 sec. (p=0.004) Average angina attacks/week: **Baseline:** Pla: 4.6 Ran 750: 4.4 Ran 1000: 4 **On treatment**: Pla 3.31 Ran 750: 2.47 (p=0.006 vs. Pla) Ran 1000: 2.11 (p=0.016 vs. Pla) Average SLNTG consumption/week: **Baseline:** Pla: 4.1 Ran 750: 4.4 Ran 1000: 3.7 **On treatment**: Pla: 3.13 Ran 750: 2.13 (p<0.001 vs. Pla) Ran 1000: 1.76 (p<0.001 vs. Pla)		Lower rate of worsening angina (4.2 vs. 5.9%) with Ran. No difference for failure of treatment or hospitalization for CHF. SAQ (Angina frequency and physical limitation dimensions) **Angina frequency:** Pla: 82.2 Ran: 84.3 (p<0.001) **Physical limitation: NS**
Safety	*Common ADEs: dizziness, nausea and asthenia and constipation. ADEs were dose-related. *Increases in QTc were dose-related with 1500 mg dose producing prolongation from 11-14 ms. *No TdP reported *Elevated eosinophil counts were observed in 6/169 patients.	*Common ADEs: constipation, dizziness, nausea, asthenia. ADEs were dose-related. *Five cases of syncope in 1000 mg group. None in 750 or pla groups. *Increases in QTc were dose-related and 6-9 ms (750 and 1000 mg, respectively) greater than pla. *No TdP reported	*Common ADEs: constipation, peripheral edema, dizziness and headache. *No cases of TdP	*Common ADEs: dizziness, nausea, constipation. *109 cases of syncope Ran vs. 75 Pla (p=0.01) *2 cases TdP-one in each group. *Holter monitoring showed less clinically significant arrhythmias on ECG including incidence of V-Tach. Since primary outcome was not met, this is only exploratory.
Comments	*Efficacy endpoints improved with higher doses. *Improvements were smaller in women	*Efficacy endpoints were not dose-related. *Background anti-anginals were sub therapeutic. *Improvements were smaller in women.	*Baseline SL NTG consumption was higher in Pla vs. Ran groups. *Patients with mean weekly angina episodes more than 4.5 were responsible for differences. *Improvements in men and women were similar but numbers of women were small.	Hierarchal research design. If primary outcome is not met, secondary outcomes can only be considered exploratory so confirmatory studies are required.

ADEs=adverse events, ETT=exercise treadmill test, HR=hazard ratio, NSTE-ACE=non-ST-segment elevation acute coronary syndrome, Pla=placebo, Ran=ranolazine, SL NTG=sublingual nitroglycerin, TdP=torsade de pointes

Comments from the FDA Medical Reviewer
There were several concerns that were expressed by the FDA medical reviewer, as follows:

- The evidence for maintaining an anti-anginal effect throughout the twice daily dosing interval of ranolazine is insufficient (concern regarding loss of anti-anginal efficacy at trough concentrations).
- No consistent treatment effect with increase in dose from 750-1000 mg.
- Insufficient data to demonstrate whether ranolazine has an effect in symptomatic patients on maximal anti-anginal therapy.
- Gender differences in improving anti-anginal efficacy.

ADVERSE EVENTS (Safety Data)

Table 3. Adverse Events Reported in Clinical Trials Involving Ranolazine

	MARISA	CARISA	ERICA	MERLIN-TIMI 36
Reported ADEs	Pla 15.6% Ran 500 16% Ran 1000 21.7% Ran 1500 34.2%	Pla 26.4% Ran 750 31.2% Ran 1000 32.7%	Pla 35% Ran 39.9%	NR
Constipation	Pla 0% Ran 500 0% Ran 1000 1.7% Ran 1500 4.3%	Pla 0.7% Ran 750 6.5% Ran 1000 7.3%	Pla 1.8% Ran 8.9%	Pla 3% Ran 9%
Dizziness	Pla 1.1% Ran 500 1.1% Ran 1000 5% Ran 1500 12.3%	Pla 1.9% Ran 750 3.6% Ran 1000 6.9%	Pla 2.5% Ran 3.9%	Pla 7% Ran 13%
Nausea	Pla 0% Ran 500 <1% Ran 1000 1.1% Ran 1500 8.6%	Pla 0.7% Ran 750 3.2% Ran 1000 5.1%	Pla 0.7% Ran 2.8%	Pla 6% Ran 9%
Asthenia	Pla 2.2% Ran 500 0% Ran 1000 1.7% Ran 1500 6.4%	Pla 2.2% Ran 750 1.8% Ran 1000 4.7%	NR	NR
Headache	Pla 2.2% Ran 500 <1% Ran 1000 1.1% Ran 1500 2.7%	Pla Ran 750 1.5% Ran 1000 2.5%	Pla 2.5% Ran 2.8%	NR
Withdraw due to ADEs	Pla n=2 Ran 500 n=1 Ran 1000 n=1 Ran 1500 n=11	NR	Pla n=4 Ran n=3	Pla 4.7% Ran 8.8%
Syncope	NR	Pla: n=0 Ran 750 n=0 Ran 1000 n=5	NR	Pla n=75 (2.3%) Ran n=109 (3.3%) (p=0.01)
QTc Increases vs. placebo (Trough/ Peak)	Ran 500 (6/5 ms) Ran 1000 (7/6 ms) Ran 1500 (11/14 ms) *QT dispersion not affected	Ran 750 6.1 ms Ran 1000 9.2 ms *QT dispersion not affected	NR	NR *Clinically sig. arrhythmia on holter monitoring: Pla n=2650 (83.1%) Ran n=2330 (73.7%) p<0.001 *Symptomatic documented arrhythmia: Pla 102 (3.1%) Ran 99 (3%) NS
Torsade de Pointes	None	None	NR	Pla n=1 Ran n=1

*****NR=not reported, NS=not significant

In all four clinical trials, examining the efficacy and safety of ranolazine SR, the rate of adverse events was higher in the ranolazine vs. placebo group. Additionally, the rate of withdrawal due to adverse events was higher in at least two of the studies. The most common adverse events were constipation, nausea, dizziness, headache and asthenia.

Deaths and Other Serious Adverse Events
The number of deaths occurring in clinical trials (sustained-release dosage forms of ranolazine) was not different between placebo and ranolazine.
QTc elevation can occur with ranolazine administration. Elevations are higher with peak ranolazine concentrations (4 hours after dosing). Baseline and follow-up electrocardiograms (ECG) should be obtained to examine the effect of ranolazine on the QT interval.

Syncope was reported more often in the ranolazine group in two of the four available trials.

Additional safety information from FDA website:
In all of the 64 clinical trials, involving both the ranolazine immediate and sustained release dosage forms in the integrated safety summary (ISS) database, 19.2% of patients on ranolazine reported syncope, symptoms suggestive of syncope or presyncope vs. patients on placebo (4.4%). The etiology of syncope associated with ranolazine is not believed to be a hemodynamic effect and will require further study.

There were small mean reductions in hemoglobin/hematocrit and small mean increases in BUN and serum creatinine, but these were considered unremarkable.

PRECAUTIONS/CONTRAINDICATIONS[1,3-4]

Precautions/Warnings

Effect on QTc Interval
Ranolazine has been shown to prolong the QT interval in a dose-dependent manner. Although the clinical significance of this effect of ranolazine is not known, other drugs prolonging the QT interval have been associated with torsades de pointes, a type of arrhythmia, and sudden death. The mean increase in QTc, associated with the 1000 mg twice daily dose of ranolazine (trough concentrations), is approximately 6 milliseconds (ms). In 5% of the population studied, the QTc was prolonged 15 ms.

Renal Impairment
In a small group of patients with severe renal impairment (Creatinine Clearance <30 ml/min and not receiving dialysis), diastolic blood pressure was increased approximately 15 mm Hg with repeat dosing of ranolazine. As a result, blood pressure should be regularly monitored in these patients.

Laboratory Tests
Increases in serum creatinine were observed in subjects receiving ranolazine (mean 0.1 mg/dl) and were reversible upon discontinuation. Changes in BUN were not observed. Renal studies, conducted to investigate ranolazine's effect on serum creatinine, showed no effect on glomerular filtration rate.

Temporary eosinophilia was infrequently noted with ranolazine. During clinical trials, small reductions in hematocrit (mean 1.2%) were observed in patients on ranolazine, with no evidence of occult blood loss.

Drug-Drug Interactions
Refer to drug-drug interaction section on pages 11 and 12 of this monograph. There are numerous drug-drug interactions to consider when prescribing ranolazine.

Contraindications
Since ranolazine has been observed to prolong the QT interval in a dose-dependent manner, its use is contraindicated in the following individuals because of the potential for a greater prolongation of the QT interval:

- Patients with pre-existing QT prolongation

- Patients with mild, moderate or severe hepatic impairment [Child-Pugh Classes A (mild), B (moderate) or C (severe)].
- Patients on QT prolonging drugs (e.g. Class Ia [quinidine] or Class III [amiodarone, dofetilide, sotalol] antiarrhythmics, erythromycin and some antipsychotic agents [thioridazine, ziprasidone]) (list is not comprehensive).[8-9]
- Patients receiving potent or moderately potent CYP 3A4 inhibiting drugs, including azole antifungals, amiodarone, macrolide antibiotics, HIV protease inhibitors, grapefruit juice, diltiazem and verapamil (list is not comprehensive).[22]

LOOK-ALIKE/SOUND-ALIKE (LA/SA) ERROR RISK POTENTIAL

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA Generic Name (Ranolazine): ranitidine 150 mg tablet, relamine tablet, rasagiline 0.5 mg tablet, rimantidine 100 mg tablet, hydralazine 37.5 mg tablet, Relasin DM liquid, sulfasalazine 500 mg tablet.

LA/SA Trade Name (Ranexa): Celexa 10, 20 and 40 mg tablets, Zyprexa 2.5-20 mg tablets, Renax 5.5 tablets, Rynesa 12S solution.

DRUG-DRUG INTERACTIONS[1, 5-7]

In vitro studies have demonstrated that ranolazine is both a substrate and an inhibitor of CYP 3A4 and P-glycoprotein (P-gp). As a result, plasma concentrations of ranolazine may be altered in the presence of inhibitors or inducers of CYP 3A4 and/or inhibitors of P-gp. Alternatively, plasma concentrations of drugs that are substrates for CYP 3A4 and/or P-gp may be altered when given concomitantly with ranolazine. Ranolazine is also metabolized to a lesser extent by CYP 2D6 and may inhibit the elimination of drugs metabolized via this route.

- **Because of the potential for increased QT prolongation with increasing plasma concentrations of ranolazine, potent or moderately potent CYP 3A4 inhibitors (e.g. azole antifungals, amiodarone, macrolide antibiotics, protease inhibitors, grapefruit juice, diltiazem, etc.) should NOT be co-administered with ranolazine. [22]**
- **Additionally, co-administration of ranolazine with other drugs known to prolong the QT interval (e.g. Class 1a and III antiarrhythmic agents [quinidine, sotalol, amiodarone, dofetilide], thioridazine, ziprasidone, macrolide antibiotics, etc.)[8-9] should be avoided in order to prevent greater QT prolongation.**

The manufacturer has conducted several drug-drug interaction studies to determine the effect of ranolazine in combination with certain drugs (see table 4).

Table 4. Results from Drug-Drug Interaction Studies with Co-Administration with Ranolazine

Precipitant Drug	Object Drug	Effect	Mechanism	Recommendation
Azole Antifungals (ketoconazole, etc.)	Ranolazine	↑ 3.2 fold	CYP 3A4 inhibition	Avoid co-administration of ranolazine with azole antifungals*
Diltiazem	Ranolazine	↑ 1.8-2.3 fold	CYP 3A4 inhibition	Avoid co-administration of diltiazem and ranolazine
Verapamil	Ranolazine	↑ 2 fold	CYP 3A4 and P-gp inhibition	Avoid co-administration of verapamil and ranolazine
Paroxetine	Ranolazine	↑ 1.2 fold	CYP 2D6 inhibition	No dose adjustment recommended**
Ranolazine	Digoxin	↑ 1.5 fold	P-gp inhibition	Reduce digoxin dose
Ranolazine	Simvastatin	↑ 2 fold	CYP 3A4 inhibition	Limit maximum daily simva dose to 40 mg or choose non CYP 3A4 metabolized statin such as fluvastatin, pravastatin or rosuvastatin
Ranolazine	Warfarin	No effect	N/A	No dose adjustment for warfarin

*Avoid co-administration of ranolazine with potent or moderately potent inhibitors of CYP 3A4 or co-administration with other QT prolonging drugs. **The manufacturer's labeling states that dose adjustments are not required when combining ranolazine with other CYP 2D6 inhibitors.

ACQUISITION COST

For the second quarter of fiscal year 2007, there were 373 unique patients on ranolazine. The average dose is 1,099 mg daily. Cost/500 mg tablet: $1.88. We are currently spending $504,892.80/year for ranolazine at current usage.

Table 5.

Drug/Dose	Cost/Day ($)	Cost/Month ($)	Cost/Year ($)
Ranolazine 500 mg twice daily	3.56	106.80	1,281.60
Ranolazine 1000 mg twice daily	7.12	213.60	2,563.20
Atenolol 100 mg	0.01	0.30	3.60
Metoprolol 100 mg BID	0.06	1.80	21.60
Metoprolol SA 200 mg (Toprol XL)	1.23	36.90	442.80
Amlodipine 10 mg	0.32	9.60	115.20
Felodipine 10 mg	0.45	13.50	162.00
Nifedipine SR 90 mg	0.33	9.90	118.80
Diltiazem SA 240 mg	0.25	7.50	90.00
Verapamil SR 240	0.07	2.10	25.20
Isosorbide dinitrate 30 mg BID or TID	0.16-0.24	4.80-7.20	57.60-86.40
Isosorbide mononitrate 120 mg	0.06	1.80	21.60
Nitroglycerin Patch 0.4 mg/hr	0.26	7.80	93.60
Atenolol 100 mg/amlodipine 10 mg/isosorbide mononitrate 120 mg	0.39	11.70	140.40

*Pricing as of 6-12-07. Generic pricing used whenever possible. Does not include tablet splitting

PHARMACOECONOMIC ANALYSIS

There are no pharmacoeconomic evaluations of ranolazine.

CONCLUSIONS

Ranolazine was approved by the FDA in January 2006 for the treatment of chronic stable angina in patients who have had an inadequate response to traditional anti-anginals. It differs from traditional anti-anginal drug therapies in that its anti-ischemic effects are independent of a hemodynamic effect (e.g. heart rate and/or blood pressure). Its effectiveness as an anti-anginal drug has been examined in three randomized, double-blind, placebo-controlled clinical trials involving nearly 1600 patients. In two of the three studies, the primary endpoint (treadmill exercise duration) was increased by about 24 seconds more than placebo (ranolazine trough concentration). At peak concentrations, exercise duration, time to angina and time to ST-segment depression was approximately 30-55 seconds more than placebo. The effect of ranolazine was not consistently improved with escalation in dose. In two of the three clinical trials evaluating the anti-anginal effect of ranolazine, mean weekly angina episodes and mean weekly consumption of SL NTG was assessed. The difference between ranolazine and placebo was about 0.3-0.6 less episodes of angina and 0-1 less SL NTG consumed per week in favor of ranolazine. However, baseline weekly angina and SL NTG consumption were 0.4-0.6 (episodes or tablets) less in the ranolazine group vs. placebo. In a subgroup analysis of the ERICA trial, patients with more than 4.5 episodes of angina per week were responsible for the statistical difference from placebo.

In a fourth study, the addition of ranolazine or placebo to standard therapy for NSTE-ACS was examined. The primary outcome was an effect on a composite outcome of CV death, MI or recurrent ischemia. There was no difference between ranolazine and placebo.

In all four clinical trials involving the sustained-release dosage form of ranolazine, adverse events were higher in the ranolazine groups vs. placebo. Additionally, the rate of withdrawal due to adverse events was higher in at least two of the studies. The most common adverse events were constipation, nausea, dizziness, headache and asthenia. Adverse events do increase with dose escalation. Ranolazine is known to increase the QT interval, has many drug-drug interactions and multiple precautions for its use. As a result, the FDA has recommended that it be used in those patients having an inadequate response with other anti-anginal drugs.

RECOMMENDATIONS/PLACE IN THERAPY

Because ranolazine is capable of prolonging the QT interval, has multiple drug-drug interactions and precautions for its use, it can be considered in those patients with chronic stable angina, having no contraindications, with an inadequate response to therapeutic doses of beta-blockers, long-acting dihydropyridine CCBs and long-acting nitrates. Additionally, patients who are not considered candidates for revascularization (PCI or CABG), are receiving maximal anti-anginal therapy and possessing no contraindications may consider use of ranolazine for their symptoms. Patients should be closely monitored for an improvement in anginal symptoms. If the patient does not feel ranolazine has improved their symptoms, it should be discontinued.

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Appendix A. Clinical Trials Involving Ranolazine in the Management of Chronic Angina

A literature search was performed on PubMed/Medline (1966 to April 2007) using the search term ranolazine, Ranexa, and chronic stable angina. The search was limited to studies performed in humans and published in English. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. Only those trials examining the efficacy and safety of the long-acting, FDA approved dosage form of ranolazine were included.

<table>
<tr><th>Study</th><th>Population</th><th>Intervention/Outcome Measures</th><th>Results</th><th>Adverse Events/Comments</th></tr>
<tr>
<td>Chaitman, et al.[14]
R, DB, MC, CO

N=191

4 weeks

(MARISA Trial)</td>
<td><u>Inclusion</u>: Subjects 21 years and older, with well documented CAD with at least a 3 month history of effort angina responding to beta-blockers, CCBs and/or long-acting nitrates. Antianginals were d/c and 2 modified Bruce ETTs were done 1 week apart. If they developed exercise limiting angina or ST-segment depression of 1 mm or more, they qualified.
<u>Exclusion</u>: Conditions that may alter ability to interpret ECG (digoxin treatment, ≥ 1 mm ST depression at rest, left bundle branch block, pacemaker), NYHA Class III or IV CHF, unstable angina, MI or coronary revascularization w/i 2 months, QTc>500 ms or on medications prolonging the QT interval or receiving food or drugs effecting metabolism of Ran.</td>
<td>After discontinuation of previous anti-anginal drugs, qualifying patients were randomized to Ran 500 mg, 1000 mg, 1500 mg or Pla twice daily for 1 week and then crossed-over to the each of the remaining Ran dosages or Pla for one week periods (for a total of 4 weeks). *After each Ran/Pla period, ETT were performed at 4 and 12 hrs after dosing (peak and trough, respectively)
<u>Primary endpoint:</u> Total exercise duration at trough conc.
<u>Other endpoints</u>: time to onset of angina, time to 1 mm ST segment depression at trough and all 3 ETT endpoints at peak conc.</td>
<td>Exercise Treadmill Test Parameters in Seconds (Mean) (n=175, 91.6% of randomized subjects completed 3 of the 4 treatment periods and were included in the primary efficacy analysis)
<table>
<tr><th>Ran/Pla</th><th>Exercise Duration (Mean difference from Pla, p-value)</th><th>Time to angina (Mean difference from Pla, p-value)</th><th>Time to 1 mm ST depression (Mean difference from Pla, p-value)</th></tr>
<tr><td>Placebo:
Trough
Peak</td><td>
505.7 s
501.7 s</td><td>
407.3 s
416.3 s</td><td>
443.3 s
436.4 s</td></tr>
<tr><td>Ran 500 mg:
Trough
Peak</td><td>
23.8 s (0.003)
29.3 s (<0.001)</td><td>
27 s (0.005)
35.5 s (<0.001)</td><td>
27.6 s (<0.001)
38.8 s (<0.001)</td></tr>
<tr><td>Ran 1000 mg:
Trough
Peak</td><td>
33.7 s (<0.001)
50.1 s (<0.001)</td><td>
45.9 s (<0.001)
56.4 s (<0.001)</td><td>
44.5 s (<0.001)
55.6 s (<0.001)</td></tr>
<tr><td>Ran 1500 mg:
Trough
Peak</td><td>
45.9 s (<0.001)
55.5 s (<0.001)</td><td>
59.6 s (<0.001)
68.5 s (<0.001)</td><td>
64.6 s (<0.001)
69 s (<0.001)</td></tr>
</table>
(Mean trough exercise duration increased 70 sec. in the Pla group, 94 in the 500 mg, 103 in the 1000 mg and 116 sec. in the 1500 mg Ran groups (all significant p<0.005). There were no significant hemodynamic changes with any dose or Ran. The two higher doses were associated with a reduction in HR and systolic BP of 3 mm Hg.</td>
<td>The most common ADEs were dizziness, nausea and asthenia and were dose-related. Nearly 8% of patients d/c treatment due to ADEs. The majority w/d from the study were on the 1500 mg dose.

Mean increase* in QTc interval
<table>
<tr><th></th><th>Trough</th><th>Peak</th></tr>
<tr><td>500 mg</td><td>6 ms</td><td>5 ms</td></tr>
<tr><td>1000mg</td><td>7 ms</td><td>6 ms</td></tr>
<tr><td>1500mg</td><td>11 ms</td><td>14 ms</td></tr>
</table>
*Mean diff vs. Pla
No patient d/c treatment because of QT prolongation >30% from baseline to a value of >500 ms. The QT dispersion was unaffected by any dose of Ran.

Elevated eosinophil counts were observed in 6/169 patients</td>
</tr>
<tr>
<td>Chaitman, et al.[15,16]
R, DB, MC, PC

N=823

12 weeks

(CARISA Trial)</td>
<td><u>Inclusion:</u> Patients with well documented CAD and a 3 month history of effort angina were enrolled if they had reproducible angina, ischemic ST-segment depression ≥ 1 mm Hg and limited exercise ability on treadmill testing (3-9 minutes Bruce Protocol) while receiving background anti-anginals.</td>
<td>Patients were randomized to receive Pla, Ran 750 mg or Ran 1000 mg twice daily for 12 weeks if they met the qualifying criteria with ETT while maintaining background fixed dose treatment with either atenolol 50 mg, amlodipine 5 mg or diltiazem SR 180 mg once daily. *ETT was</td>
<td>Results: (Mean trough exercise duration increased 91.7 s in the Pla group vs. 115.6 s in the pooled Ran groups, p<0.01)
<table>
<tr><th>Variable</th><th>Ran 750 (Mean difference from Pla, p-value, 95% CI)</th><th>Ran 1000 (Mean difference from Pla, p-value, 95% CI)</th></tr>
<tr><td><u>Exercise Duration</u>
Trough</td><td>
23.7 s (0.03, 2.3-45.1)</td><td>
24 s (0.03, 2.4-45.7)</td></tr>
</table>
</td>
<td>*In CARISA, there was not an apparent dose-response.
*Ranolazine increased exercise duration and time to angina at both peak and trough Ran conc. vs. Pla. However, there was no difference in time to 1mm ST depression at Ran trough conc. suggesting an inadequate inter-</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>Exclusion: Conditions that may alter ability to interpret ECG (digoxin treatment, ≥ 1 mm ST depression at rest, left bundle branch block, pacemaker), NYHA Class III or IV CHF, ACS or coronary revascularization w/i prior 2 months, use of grapefruit juice, significant valvular/congenital heart disease, on meds known to prolong QT interval</td>
<td>performed at trough conc (12 hrs after dosing at 2, 6 and 12 weeks and at peak conc. (4 hrs after dose) at weeks 2 and 12.
Primary endpoint: Effect of ranolazine on treadmill exercise duration at trough conc.
Other endpoints: time to onset of angina, time to 1 mm ST segment depression at trough and all 3 ETT endpoints at peak conc. Also, self-reported angina attacks and SL nitro uses reported in patient daily diaries</td>
<td>
<table>
<tr><td>Peak</td><td>34 s (0.001)</td><td>26.1 s (0.02)</td></tr>
<tr><td>Time to angina</td><td></td><td></td></tr>
<tr><td>Trough</td><td>29.7 s (0.01)</td><td>26 S (0.03)</td></tr>
<tr><td>Peak</td><td>38 s (0.002)</td><td>37.9 s (0.003)</td></tr>
<tr><td>Time to 1 mm ST depression</td><td></td><td></td></tr>
<tr><td>Trough</td><td>19.9 s (0.1)</td><td>21.1 s (0.09)</td></tr>
<tr><td>Peak</td><td>40.8 s (<0.001)</td><td>34.5 s (0.004)</td></tr>
</table>
Background antianginals: atenolol (n=354, 43%), amlodipine (n=256, 31.1%), diltiazem (n=213, 25.9%)

Angina attacks/NTG use per week (FDA website)
<table>
<tr><th>Group</th><th>Angina Attacks/ Week (Mean baseline/on-treatment)</th><th>NTG/Week (Mean baseline/on-treatment)</th></tr>
<tr><td>Pla</td><td>4.6/3.31</td><td>4.1/3.14</td></tr>
<tr><td>Ran 750</td><td>4.4/2.47 (p vs. Pla 0.006)</td><td>4.4/2.13 (p vs. Pla <0.001)</td></tr>
<tr><td>Ran 1000</td><td>4/2.11 (p vs. Pla 0.016)</td><td>3.7/1.76 (p vs. Pla <0.001)</td></tr>
</table>
Although the majority of subjects were male (approx. 75%), a subgroup analysis presented to the FDA did not show a significant treatment effect for the primary endpoint in women (no difference vs. Pla) and possibly less of an effect in the elderly (>65) and in those with CHF but the study was not powered for these groups. There did not appear to be a rebound effect after d/c therapy with Ran. (e.g. worsening angina or increased NTG use).
</td>
<td>dosing interval.
*A reviewer with the FDA commented that one site had highly significant results and when the data were analyzed, excluding this site, the differences in exercise duration in the Ran vs. Pla groups were small and not statistically significant.
*There were no differences in death. There were 5 cases of syncope reported, all receiving the 1000 mg Ran dose and 4/5 receiving background diltiazem. No cases of TdP were reported.
*The most common ADEs were constipation, dizziness, nausea and asthenia. The authors did not provide reasons for exclusion of approx. 10% of patients in each group from the efficacy analysis. The FDA website was accessed for this information. Unacceptable ADEs were the reason for w/d in 13 Pla, 20 Ran 750 and 24 Ran 1000 pts.
*Dose-related increases in QTc were noted in the Ran vs. Pla groups, 6.1 and 9.2 ms, respectively. Ran did not effect QT dispersion.</td>
</tr>
<tr>
<td>Stone, et al[17]
R, DB, MC, PC

(n= 565)

6 weeks</td>
<td>Inclusion: 18 years and older, documented CAD, chronic stable angina for 3 months or more, 3 or more episodes of angina/week during a 2-week qualification period while receiving amlodipine. Long-acting nitrates (LAN) could</td>
<td>Patients who had 3 or more episodes of angina/week during the 2 week qualifying phase (amlodipine 10 mg/d) were randomized to receive Ran 500 mg BID for 1 week, increased to 1000 mg BID for 6 weeks or Pla.</td>
<td>98% of patients in each group completed the trial. Although not statistically different, more Ran/amlodipine patients were receiving LANs vs. Pla/amlodipine (46 vs. 43%, respectively) and weekly rate of NTG SL use was also higher in the Pla group (5.02 vs. 4.43 Ran).</td>
<td>ADEs were reported in 35.3% Pla vs. 39.9% Ran subjects. There were no serious ADEs in either group. Constipation (8.9% Ran, 1.8% Pla), peripheral edema (5.7 % Ran vs. 2.8% Pla), dizziness (2.8%</td>
</tr>
</table>

<table>
<tr>
<td>ERICA Trial</td>
<td>be continued.
Exclusion: NYHA class IV CHF, ACS w/i prior 2 months, uncontrolled HTN, h/o TdP, on other QT prolonging drugs, QTc >500 ms, drugs inhibiting CYP 3A4, hepatic disease or CrCl <30 ml/min, etc.</td>
<td>Primary endpoint: Weekly average frequency of self-reported episodes of angina. Endpoint was assessed at weeks 2 and 6.
Other endpoints: Average weekly NTG consumption rate and the change from baseline in the 5 dimensions of the Seattle Angina Questionnaire (SAQ) (angina frequency, physical limitation, anginal stability, disease perception and treatment satisfaction, rated 0-100)</td>
<td>
<table>
<tr><th>Variable</th><th>Placebo (SE)</th><th>Ranolazine (SE)</th><th>p-value</th></tr>
<tr><td>Weekly Angina Frequency:
Baseline
Trimmed mean
Arithmetic mean
25th percentile
Median
75th percentile</td><td>
5.68 ± 0.26
3.31 ± 0.22
4.30 ± 0.64
1.47
2.43
4.17</td><td>
5.59 ± 0.21
2.88 ± 0.19
3.29 ± 0.26
1.24
2.18
3.66</td><td>0.028 (p-value only provided for trimmed mean)</td></tr>
<tr><td>Weekly NTG Consumption:
Baseline
Trimmed mean
Arithmetic mean
25th percentile
Median
75th percentile</td><td>
5.02 ± 0.33
2.68 ± 0.22
3.57 ± 0.54
0.5
1.67
4</td><td>
4.43 ± 0.26
2.03 ± 0.2
2.72 ± 0.38
0.47
1.34
2.48</td><td>0.014 (only provided for trimmed mean)</td></tr>
<tr><td>SAQ
Angina frequency
Physical limitation
Angina Stability
Disease Perception
Treatment Satisfaction</td><td>
18.5 ± 18.8
ND
ND
ND
ND</td><td>
22.5 ± 19
ND
ND
ND
ND</td><td>0.008 significant difference only for angina frequency and not the other dimensions</td></tr>
</table>
*Trimmed mean was defined as averaging all but the top and bottom 2% of responders in an attempt to limit the influence of the outliers.

Subgroup: Results by Severity of Angina
<table>
<tr><th>Variable</th><th>≤ 4.5 angina episodes/week (p-value)</th><th>>4.5 angina episodes/week (p-value)</th></tr>
<tr><td>Angina Frequency*</td><td>0.036</td><td>0.029</td></tr>
<tr><td>NTG Consumption*</td><td>0.28</td><td><0.001</td></tr>
<tr><td>SAQ-Angina frequency</td><td>0.57</td><td><0.001</td></tr>
</table>
*Using trimmed mean, vs. Pla
Subgroup analyses: gender, age, LAN. Treatment effect did not appear to be different within these subgroups but the study was not powered for these subgroup analyses.
</td>
<td>Ran vs. 0.7% Pla) and headache were the most common ADEs. No cases of TdP were reported. There was one death in each group.</td>
</tr>
</table>

<table>
<tr>
<td>Morrow, et al[18-19]
R, DB, MC, PC

(n=6560)

Median 348 days

MERLIN-TIMI 36 Trial</td>
<td>Inclusion: 18 years or older, hospitalized with NSTE-ACS (chest discomfort or anginal equivalent occurring at rest, lasting 10 or more minutes and consistent with myocardial ischemia and present within past 48 hrs) and at least one indicator of moderate to high risk (elevated cardiac troponin or CK-MB, ST depression ≥0.1 mV, DM, TIMI risk score for UA/NSTEMI ≥3.
Exclusion: ST segment elevation >0.1 mV in 2 contiguous leads, revascularization prior to randomization, cardiogenic shock, LBBB, pacemaker or LVH, use of strong CYP 3A4 inhibitors, use of agents known to prolong QT, use of digoxin, hepatic disease, end stage renal disease requiring dialysis.</td>
<td>Patients presenting with NSTE-ACS were randomized to Ran or Pla and followed for a minimum of 6 months and average of 12 months. Intravenous Ran was used for 12-96 hrs to rapidly achieve and maintain adequate plasma conc. followed by oral doses of 1000 mg BID. Doses could be reduced for ADEs.
*Randomization was stratified by physician's intended initial management strategy, early invasive vs. conservative.
Primary endpoint: First occurrence of any element of the composite of CV death, MI or recurrent ischemia. (If the null hypothesis of the primary endpoint is not rejected, secondary analyses are considered only exploratory).
Secondary endpoint: First occurrence of a major CV event (composite of CV death, MI or severe recurrent ischemia [ischemia with ECG changes, ischemia leading to hosp., worsening angina requiring additional therapy]).
Others included failure of therapy, QOL using SAQ (angina frequency and physical limitation dimensions and assessment of first 30 days (CV death, MI or severe recurrent ischemia, or positive holter for ischemia).
A holter monitor was in place for the first 7 days.
Study visits: 14 days, 4 months and every 4 months thereafter.</td>
<td>6560 patients were included in intent to treat analysis.

<table>
<tr><th>Variable</th><th>Pla (%)</th><th>Ran (%)</th></tr>
<tr><td>ASA</td><td>96</td><td>96.2</td></tr>
<tr><td>Beta-blocker</td><td>89.7</td><td>88.7</td></tr>
<tr><td>Statin</td><td>82</td><td>82.7</td></tr>
<tr><td>Index event:
UA
NSTEMI
Other</td><td>
46.5
50.8
2.7</td><td>
47
51.1
1.9</td></tr>
</table>
*Qualifying ACS managed with medical therapy alone (60.5%), PCI (31.6%), and CABG (7.9%)
Efficacy outcomes from randomization to end of study
<table>
<tr><th>Endpoint</th><th>Pla (%)</th><th>Ran (%)</th><th>Statistics (Hazard ratio, 95% CI, P-value)</th></tr>
<tr><td>Primary</td><td>753 (23.5)</td><td>696 (21.8)</td><td>0.92 (0.83-1.02), 0.11</td></tr>
<tr><td>Major Secondary</td><td>625 (19.2)</td><td>602 (18.7)</td><td>0.96 (0.86-1.08), 0.5</td></tr>
<tr><td>CV Death</td><td>148 (4.5)</td><td>147 (4.4)</td><td>1 (0.79-1.25), 0.98</td></tr>
<tr><td>MI</td><td>242 (7.6)</td><td>235 (7.4)</td><td>0.97 (0.81-1.16), 0.76</td></tr>
<tr><td>Recurrent Ischemia
ECG changes
Hospitalization
Revascularization
Worse angina</td><td>
143 (4.7)
279 (8.8)
168 (5.3)
175 (5.9)</td><td>
126 (4.1)
247 (8)
142 (4.6)
135 (4.5)</td><td>95% CI only

0.69-1.12
0.75-1.05
0.67-1.05
0.62-0.97</td></tr>
<tr><td>Failure of Tx</td><td>1233 (38.3)</td><td>1173 (36.8)</td><td>0.94 (0.87-1.02), 0.16</td></tr>
<tr><td>Hosp for CHF</td><td>135 (4.2)</td><td>141 (4.5)</td><td>1.05 (0.83-1.33), 0.68</td></tr>
</table>
* Subgroup analysis did not show any heterogeneity of results among the subgroups studied including women and early invasive vs. conservative management.
Efficacy outcomes from randomization to 30 days (prespecified)
<table>
<tr><th>Endpoint</th><th>Pla</th><th>Ran</th><th>Statistics (Hazard ratio, 95% CI, P-value)</th></tr>
<tr><td>CV death, MI, severe ischemia,</td><td>824 (25.1)</td><td>757 (23.1)</td><td>0.92 (0.84-1),</td></tr>
</table>
</td>
<td>In the design and rationale, the investigators stated that if there was no difference in the primary outcome, all subsequent efficacy analyses were to be considered exploratory.

*28% of Ran subjects w/d from study vs. 22% Pla. Of those w/d early, 31% of Ran and 21% of Pla w/d due to ADEs. Or, 8.8% of Ran subjects vs. 4.7% of Pla subjects (p<0.001).
*The most common ADEs: dizziness (13% Ran, 7% Pla), nausea (9% Ran, 6% Pla) and constipation (9% Ran, 3% Pla).
*109 cases of syncope occurred in the Ran group (3.3%) vs. 75 in the Pla group (2.3%, p=0.01)
*Two cases of TdP were identified, one in each group.

*At the end of the study, 83% of Ran subjects were taking 1000 mg BID, 6%-750 mg BID, 7%-500 mg BID, 2%-375 mg BID and 2% never took a dose.</td>
</tr>
</table>

+ Holter for ischemia			0.055
CV Death	50 (1.5)	57 (1.7)	1.14 (0.78-1.66), 0.49
MI	114 (4)	90 (2.7)	0.79 (0.6-1.04), 0.09
Severe recurrent Ischemia	131 (4)	121 (3.7)	0.92 (0.73-1.18), 0.52
Positive Holter for ischemia	658 (21)	613 (19.9)	0.93 (0.84-1.04), 0.21

SAQ Scores: Angina Frequency improved to 84.3 on Ran vs. 82.2 on Pla ($p<0.001$). The physical limitation dimension was not significantly different.

Major Safety Outcomes

Outcome	Pla (%)	Ran (%)	Statistics (Hazard ratio, 95% CI, P-value)
Death from any Cause	175 (5.3)	172 (5.3)	0.99 (0.8-1.22), 0.91
Death or CV Hospitalization	1082 (33.4)	1046 (33.2)	0.97 (0.89-1.06), 0.53
Symptomatic, documented arrhythmia	102 (3.1)	99 (3)	0.84 (p-value)
Clinically significant arrhythmia on Holter Monitor	2650 (83.1)	2330 (73.7)	<0.001 (p-value)
Incidence of V-Tach on Holter	1211 (38)	948 (30)	<0.001 (p-value)

Safety outcomes: death from any cause, composite of death or any CV hospitalization, incidence of symptomatic documented arrhythmia or significant arrhythmia on holter monitor in those 7 days.

ACS=acute coronary syndrome, ADEs=adverse events, DB=double-blind, d/c=discontinue, DM=diabetes mellitus, CAD=coronary artery disease, CCBs=calcium channel blockers, CO=cross-over, ECG=electrocardiogram, ETT=exercise treadmill test, LAN=long-acting nitrates, LBBB=left bundle branch block, LVH=left ventricular hypertrophy, MC=multicenter, ms=milliseconds, ND=not different from placebo, NSTE-ACS=non-ST segment elevation-acute coronary syndrome, NSTEMI=non-ST segment elevation MI, NTG=nitroglycerin sl, Pla=placebo, QTc=QT interval corrected, R=randomized, Ran=ranolazine, , SAQ=Seattle Angina Questionnaire, SE=standard error, SL=sublingual, TdP=torsades de pointes, UA=unstable angina, w/d=withdraw, w/i=within