

Key Cardiac Magnetic Resonance Changes Within 6 Months of CPAP

	Baseline	Follow-up
Left ventricular end-systolic volume	68 mL	53 mL
Left ventricular end-diastolic volume	199 mL	150 mL
Left ventricular mass	184 g	149 g
Left atrial volume index	49 mL/m ²	34 mL/m ²

Notes: Based on a study of 32 patients with moderate to severe obstructive sleep apnea. All reductions are statistically significant.

Source: Dr. Al-Mutairi



Brief Summary of Prescribing Information

These highlights do not include all the information needed to use Ranexa safely and effectively. See full prescribing information for Ranexa.

Ranexa (ranolazine) extended-release tablets

1. INDICATIONS AND USAGE

Ranexa is indicated for the treatment of chronic angina.

Ranexa may be used with beta-blockers, nitrates, calcium channel blockers, anti-platelet therapy, lipid-lowering therapy, ACE inhibitors, and angiotensin receptor blockers.

2. DOSAGE AND ADMINISTRATION

2.1 Dosing Information

Initiate Ranexa dosing at 500 mg twice daily and increase to 1000 mg twice daily, as needed, based on clinical symptoms. Take Ranexa with or without meals. Swallow Ranexa tablets whole; do not crush, break, or chew.

The maximum recommended daily dose of Ranexa is 1000 mg twice daily.

If a dose of Ranexa is missed, take the prescribed dose at the next scheduled time; do not double the next dose.

2.2 Dose Modification

Dose adjustments may be needed when Ranexa is taken in combination with certain other drugs [see Drug Interactions (7.1)]. Limit the maximum dose of Ranexa to 500 mg twice daily in patients on diltiazem, verapamil, and other moderate CYP3A inhibitors. Down-titrate Ranexa based on clinical response in patients concomitantly treated with P-gp inhibitors, such as cyclosporine.

3. DOSAGE FORMS AND STRENGTHS

Ranexa is supplied as film-coated, oblong-shaped, extended-release tablets in the following strengths:

- 500 mg tablets are light orange, with GS1500 on one side
- 1000 mg tablets are pale yellow, with GS11000 on one side

4. CONTRAINDICATIONS

Ranexa is contraindicated in patients:

- Taking strong inhibitors of CYP3A [see Drug Interactions (7.1)]
- Taking inducers of CYP3A [see Drug Interactions (7.1)]
- With clinically significant hepatic impairment [see Use in Specific Populations (8.6)]

5. WARNINGS AND PRECAUTIONS

5.1 QT Interval Prolongation: Ranolazine blocks I_{Ca} and prolongs the QTc interval in a dose-related manner.

Clinical experience in an acute coronary syndrome population did not show an increased risk of proarrhythmia or sudden death. However, there is little experience with high doses (> 1000 mg twice daily) or exposure, other QT-prolonging drugs, or potassium channel variants resulting in a long QT interval.

6. ADVERSE REACTIONS

6.1 Clinical Trial Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 2,018 patients with chronic angina were treated with ranolazine in controlled clinical trials. Of the patients treated with Ranexa, 1,026 were enrolled in three double-blind, placebo-controlled, randomized studies (CARISA, ERICA, MARISA) of up to 12 weeks duration. In addition, upon study completion, 1,251 patients received treatment with Ranexa in open-label, long-term studies; 1,227 patients were exposed to Ranexa for more than 1 year, 613 patients for more than 2 years, 531 patients for more than 3 years, and 326 patients for more than 4 years.

At recommended doses, about 6% of patients discontinued treatment with Ranexa because of an adverse event in controlled studies in angina patients compared to about 3% on placebo. The most common adverse events that led to discontinuation more frequently on Ranexa than placebo were dizziness (1.3% versus 0.1%), nausea (1% versus 0%), asthenia, constipation, and headache (each about 0.5% versus 0%). Doses above 1000 mg twice daily are poorly tolerated.

In controlled clinical trials of angina patients, the most frequently reported treatment-emergent adverse reactions (> 4% and more common on Ranexa than on placebo) were dizziness (6.2%), headache (5.5%), constipation (4.5%), and nausea (4.4%). Dizziness may be dose-related. In open-label, long-term treatment studies, a similar adverse reaction profile was observed.

The following additional adverse reactions occurred at an incidence of 0.5 to 2.0% in patients treated with Ranexa and were more frequent than the incidence observed in placebo-treated patients:

Cardiac Disorders – bradycardia, palpitations

Ear and Labyrinth Disorders – tinnitus, vertigo

Gastrointestinal Disorders – abdominal pain, dry mouth, vomiting

General Disorders and Administrative Site Adverse Events – peripheral edema

Respiratory, Thoracic, and Mediastinal Disorders – dyspnea

Vascular Disorders – hypotension, orthostatic hypotension

Other (< 0.5%) but potentially medically important adverse reactions observed more frequently with Ranexa than placebo treatment in all controlled studies included: angioedema, renal failure, eosinophilia, blurred vision, confusional state, hematuria, hyposesthesia, paresthesia, tremor, pulmonary fibrosis, thrombocytopenia, leukopenia, and pancytopenia.

A large clinical trial in acute coronary syndrome patients was unsuccessful in demonstrating a benefit for Ranexa, but there was no apparent proarrhythmic effect in these high-risk patients.

Laboratory Abnormalities

Ranexa produces small reductions in hemoglobin A1c. Ranexa is not a treatment for diabetes.

Ranexa produces elevations of serum creatinine by 0.1 mg/dL, regardless of previous renal function. The elevation has a rapid onset, shows no signs of progression during long-term therapy, is reversible after discontinuation of Ranexa, and is not accompanied by changes in BUN. In healthy volunteers, Ranexa 1000 mg twice daily had no effect upon the glomerular filtration rate. The elevated creatinine levels are likely due to a blockage of creatinine's tubular secretion by ranolazine or one of its metabolites.

7. DRUG INTERACTIONS

7.1 Effects of Other Drugs on Ranolazine: Ranolazine is primarily metabolized by CYP3A and is a substrate of P-glycoprotein (P-gp).

CYP3A Inhibitors

Do not use Ranexa with strong CYP3A inhibitors, including ketoconazole, itraconazole, clarithromycin, nefazodone, nefinavir, ritonavir, indinavir, and saquinavir. Ketoconazole (200 mg twice daily) increases average steady-state plasma concentrations of ranolazine 3.2-fold [see Contraindications (4)].

Limit the dose of Ranexa to 500 mg twice daily in patients on moderate CYP3A inhibitors, including diltiazem, verapamil, aprepitant, erythromycin, fluconazole, and grapefruit juice or grapefruit-containing products. Diltiazem (180–360 mg daily) and verapamil (120 mg three times daily) increase ranolazine steady-state plasma concentrations about 2-fold [see Dosage and Administration (2.2)].

Weak CYP3A inhibitors such as simvastatin (20 mg once daily) and cimetidine (400 mg three times daily) do not increase the exposure to ranolazine in healthy volunteers.

P-gp Inhibitors

Down-titrate Ranexa based on clinical response in patients concomitantly treated with P-gp inhibitors, such as cyclosporine [see Dosage and Administration (2.2)].

CYP3A and P-gp Inducers

Avoid co-administration of Ranexa and CYP3A inducers such as rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, and St. John's wort. Rifampin (600 mg once daily) decreases the plasma concentration of ranolazine (1000 mg twice daily) by approximately 95% by induction of CYP3A and, probably, P-gp.

CYP2D6 Inhibitors

The potent CYP2D6 inhibitor, paroxetine (20 mg once daily), increases ranolazine concentrations 1.2-fold. No dose adjustment of Ranexa is required in patients treated with CYP2D6 inhibitors.

Digoxin

Digoxin (0.125 mg) does not significantly alter ranolazine levels.

7.2 Effects of Ranolazine on Other Drugs: *In vitro* studies indicate that ranolazine and its O-demethylated metabolite are weak inhibitors of CYP3A, moderate inhibitors of CYP2D6 and moderate P-gp inhibitors. Ranolazine and its most abundant metabolites are not known to inhibit the metabolism of substrates for CYP 1A2, 2C8, 2C9, 2C19, or 2E1 in human liver microsomes, suggesting that ranolazine is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes.

Drugs Metabolized by CYP3A

The plasma levels of simvastatin, a CYP3A substrate, and its active metabolite are each increased about 2-fold in healthy subjects receiving simvastatin (80 mg once daily) and Ranexa (1000 mg twice daily). Dose adjustments of simvastatin are not required when Ranexa is co-administered with simvastatin.

The pharmacokinetics of diltiazem is not affected by ranolazine in healthy volunteers receiving diltiazem 60 mg three times daily and Ranexa 1000 mg twice daily.

Drugs Transported by P-gp

Ranexa (1000 mg twice daily) causes a 1.5-fold elevation of digoxin plasma concentrations. The dose of digoxin may have to be adjusted.

Drugs Metabolized by CYP2D6

Ranolazine or its metabolites partially inhibit CYP2D6. There are no studies of concomitant use of Ranexa with other drugs metabolized by CYP2D6, such as tricyclic antidepressants and antipsychotics, but lower doses of CYP2D6 substrates may be required.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy—Pregnancy Category C: In animal studies, ranolazine at exposures 1.5 (rabbit) to 2 (rat) times the usual human exposure caused maternal toxicity and misshapen sternbrae and reduced ossification in offspring. These doses in rats and rabbits were associated with an increased maternal mortality rate. There are no adequate well-controlled studies in pregnant women. Ranexa should be used during pregnancy only when the potential benefit to the patient justifies the potential risk to the fetus.

8.3 Nursing Mothers: It is not known whether ranolazine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from ranolazine in nursing infants, decide whether to discontinue nursing or to discontinue Ranexa, taking into account the importance of the drug to the mother.

8.4 Pediatric Use: Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use: Of the chronic angina patients treated with Ranexa in controlled studies, 496 (48%) were ≥ 65 years of age, and 114 (11%) were ≥ 75 years of age. No overall differences in efficacy were observed between older and younger patients. There were no differences in safety for patients ≥ 65 years compared to younger patients, but patients ≥ 75 years of age on ranolazine, compared to placebo, had a higher incidence of adverse events, serious adverse events, and drug discontinuations due to adverse events. In general, dose selection for an elderly patient should usually start at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease, or other drug therapy.

8.6 Use in Patients with Hepatic Impairment: Ranexa is contraindicated in patients with clinically significant hepatic impairment. Plasma concentrations of ranolazine were increased by 30% in patients with mild (Child-Pugh Class A) and by 60% in patients with moderate (Child-Pugh Class B) hepatic impairment. This was not enough to account for the 3-fold increase in QT prolongation seen in patients with mild to severe hepatic impairment [see Contraindications (4)].

8.7 Use in Patients with Renal Impairment: In patients with varying degrees of renal impairment, ranolazine plasma levels increased up to 50%. The pharmacokinetics of ranolazine has not been assessed in patients on dialysis.

8.8 Use in Patients with Heart Failure: Heart failure (NYHA Class I to IV) had no significant effect on ranolazine pharmacokinetics. Ranexa had minimal effects on heart rate and blood pressure in patients with angina and heart failure NYHA Class I to IV. No dose adjustment of Ranexa is required in patients with heart failure.

8.9 Use in Patients with Diabetes Mellitus: A population pharmacokinetic evaluation of data from angina patients and healthy subjects showed no effect of diabetes on ranolazine pharmacokinetics. No dose adjustment is required in patients with diabetes.

Ranexa produces small reductions in HbA1c in patients with diabetes, the clinical significance of which is unknown. Ranexa should not be considered a treatment for diabetes.

10. OVERDOSAGE

High oral doses of ranolazine produce dose-related increases in dizziness, nausea, and vomiting. High intravenous exposure also produces diplopia, paresthesia, confusion, and syncope. In addition to general supportive measures, continuous ECG monitoring may be warranted in the event of overdose.

Since ranolazine is about 62% bound to plasma proteins, hemodialysis is unlikely to be effective in clearing ranolazine.

Please see full prescribing information at www.Ranexa.com.

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc, at 1-800-GILEAD-5, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Rx only

Manufactured for: Gilead Sciences, Inc, Foster City, CA 94404 USA

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CPAP Reversed Atrial, Ventricular Remodeling

BY BRUCE JANCIN

FROM THE ANNUAL MEETING OF THE ASSOCIATED PROFESSIONAL SLEEP SOCIETIES

SAN ANTONIO — Six months of continuous positive airway pressure therapy markedly improved adverse left ventricular and atrial remodeling in patients with moderate to severe obstructive

sleep apnea in a prospective study.

Diastolic as well as systolic abnormalities were reversed, raising the welcome prospect that CPAP is likely to prevent the development of one of the most dreaded complications of severe obstructive sleep apnea (OSA)—chronic heart failure—although this point remains speculative, Dr. Saleh Al-Mutairi said.

He recruited 32 patients with newly diagnosed moderate to severe OSA for the study, which involved serial follow-up by cardiac magnetic resonance (CMR), echocardiography, and cardiac biomarkers through 6 months of individually titrated CPAP therapy.

The subjects averaged 51 years of age, with a mean baseline apnea-hypopnea index of 53 events/hr and a body mass index of 34.5 kg/m². None of the participants had known cardiac disease. Adherence to CPAP was good. The patients' weight didn't change significantly during the study, and those being treated for hypertension remained on the same doses of medication throughout the follow-up period.

Other studies have shown improvement in left ventricular dysfunction with CPAP, but they were short-term trials. This is the first study with follow-up as long as 6 months using both CMR and echocardiography, according to Dr. Al-Mutairi of the University of Manitoba, Winnipeg.

He focused on the CMR results because he considers that technology more reliable than echocardiography for assessing ventricular size and function. The echo findings, however, corroborated the CMR results.

Most of the left ventricular measurements followed during the study were abnormal at baseline. The 6-month results included a 25% reduction from baseline in left ventricular end-diastolic volume and a 19% decrease in left ventricular mass. (See chart.)

Dr. Al-Mutairi drew particular attention to the 30% reduction in left atrial volume index, which he considers highly encouraging. "This is a very important point, given the association between the left atrial volume and cardiovascular events," he observed.

There was no significant change in C-reactive protein, brain natriuretic peptide, or other cardiac biomarkers during the 6 months of CPAP use.

The mechanism by which OSA is thought to predispose to heart failure involves an exaggerated negative thoracic pressure in response to the apneic episodes. This presumably leads to increased left ventricular systolic transmural pressure, which the left atrium resists, with resultant increased compliance and atrial overstretching, Dr. Al-Mutairi said.

He and his coinvestigators are in the midst of expanding their study to 50 patients in order to strengthen the conclusions. ■

Disclosures: Dr. Al-Mutairi reported having no financial conflicts.