



# CIGNA PHARMACY COVERAGE POLICY

*This Coverage Policy should NOT be used for Great-West benefit plans.*

Effective Date ..... 4/15/2009  
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Coverage Policy Number ..... 6113

Subject **Ranolazine (Ranexa®)**

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## Hyperlink to Related Coverage Policies

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2009 CIGNA

## Coverage Policy

**CIGNA covers ranolazine (Ranexa®) as medically necessary for the treatment of chronic angina when there is a failure, contraindication, or intolerance to two classes of antianginal therapeutic alternatives (i.e., nitrates, beta-blockers, calcium channel blockers).**

## General Background

### FDA Approved Indications

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.

### FDA Recommended Dosing

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.

Ranolazine is an extended-release anti-ischemic and antianginal drug, designed to act without reducing heart rate or blood pressure. Ranexa is specifically indicated for the treatment of chronic angina in patients who have failed to respond to prior angina therapies. Ranolazine is the first metabolic modulator approved for the treatment of chronic angina. Due to QTc prolongation, ranolazine is only recommended in patients who have not achieved an adequate response with or who are unresponsive to other antianginal drugs. Ranolazine should be used in combination with other antianginal medications such as calcium channel blockers, beta-blockers, or nitrates.

The mechanism of action of ranolazine has not been determined. Ranolazine has antianginal and anti-ischemic effects that do not depend upon reductions in heart rate or blood pressure. Ranolazine at therapeutic levels can inhibit the late  $I_{NA}$ , however, the relationship of this inhibition to angina symptoms is uncertain. The QT prolongation effect of ranolazine on the surface electrocardiogram is the result of inhibition of  $I_{Kr}$ , which prolongs the ventricular action potential.

Absorption of ranolazine is highly variable. Peak plasma concentrations are reached within two to five hours, and steady state is reached within three days after initiating therapy. Bioavailability is 76%, and it is 62% bound to plasma proteins. Ranolazine is excreted in the urine (75%) and feces (25%). Ranolazine is metabolized by CYP3A and to a lesser extent by the CYP2D6 enzymes. The half-life of ranolazine is approximately seven hours. Moderate hepatic impairment and renal impairment of all severities affect the pharmacokinetics of ranolazine by increasing ranolazine concentrations.

Three randomized, placebo-controlled, multicentered trials have evaluated the efficacy of extended-release ranolazine. In the ERICA and CARISA trials, ranolazine decreased angina episodes by 23% to 36% and decreased nitroglycerin use by 25% to 42% compared to placebo. In addition, the CARISA and MARISA trials showed ranolazine to have an increase in exercise duration of 20.5 to 45.9 seconds with trough concentrations compared to placebo. Ranolazine may be less effective in women compared to men, although this is controversial.

In August 2007, the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) added ranolazine to the revised guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI). This addition was based on the results of a randomized, double-blind, placebo-controlled, large multinational clinical trial (Morrow et al. 2007) in 6,560 patients within 48 hours of ischemic symptoms who were treated with ranolazine (n=3279) or placebo (n=3281). The objective of this study was to evaluate the efficacy and safety of ranolazine during long-term treatment of patients with non-ST-elevation acute coronary syndromes (ACS). The primary efficacy end point of the study was a composite of cardiovascular death, myocardial infarction (MI), or recurrent ischemia through the end of study. Results showed that the addition of ranolazine to standard treatment for ACS is safe and effective as antianginal therapy but not effective in reducing major cardiovascular events as it did not achieve the primary efficacy end point. Therefore, ranolazine may be safely administered for symptom relief after UA/NSTEMI, but it does not appear to significantly improve the underlying disease substrate.

The most common adverse drug reactions with ranolazine are dizziness, headache, and nausea. The most serious adverse drug reaction is QTc prolongation which, on average, increases the QTc interval by five to nine milliseconds. The frequency of adverse drug reactions increases as the dose of ranolazine increases. Side effects are more common in patients who are 75 years old or older and in patients with renal impairment.

Ranolazine affects the cytochrome P450 enzyme system by inhibiting the CYP3A and CYP2D6 enzymes. Ranolazine is also a substrate for CYP3A. Because of this, there are multiple drug interactions. Do not co-administer ranolazine with moderate to strong CYP3A inhibitors. No dosage adjustments are necessary for CYP2D6 inhibitors. Lower doses of CYP2D6 substrates such as tricyclic antidepressants and antipsychotics may be required with ranolazine co-administration. In addition to the effects on liver enzymes, ranolazine is a P-glycoprotein (P-gp) inhibitor. Use caution when administering ranolazine along with other P-gp inhibitors. Ranolazine should not be co-administered with other medications which prolong the QTc interval.

Ranolazine is contraindicated in patients with pre-existing QT prolongation, hepatic impairment, or potent and moderately potent CYP3A inhibitors, including diltiazem. Ranolazine has been shown to prolong the QT interval in a dose-related manner. Other drugs with this potential have been associated with torsades de pointes such as arrhythmias and sudden death. Concurrent use of other QT prolonging drugs is also contraindicated, especially in patients with hepatic dysfunction where QT prolongation is enhanced. In addition, Ranolazine has been shown to increase digoxin plasma levels 1.5 fold. Reduced doses of digoxin and simvastatin may be required in patients receiving ranolazine.

Ranolazine is the first metabolic modulator for the treatment of chronic angina. Due to QTc prolongation, ranolazine is only recommended in patients who have not achieved an adequate response or who are unresponsive to other antianginal medications. Ranolazine should be used in combination with other antianginal medications. Ranolazine increases exercise duration, increases time to exercise-induced angina, and decreases angina frequency. Ranolazine is not indicated in patients with a history of QTc prolongation, in patients taking medications known to prolong the QTc interval, or in patients with hepatic impairment. Ranolazine provides a therapeutic option for patients who have not achieved adequate response with other antianginal medications and in patients where a decrease in heart rate or blood pressure is not desired.

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## Coding/Billing Information

**Note:** This section is not in use

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