CVT | CV Therapeutics®

Ranexa® RANOLAZINE EXTENDED-RELEASE TABLETS 500 mg · 1000 mg

Dear Pharmacist,

CV Therapeutics, Inc. is very pleased to announce that the U.S. Food and Drug Administration (FDA) recently approved new labeling for Ranexa® (ranolazine extended-release tablets) as an initial therapeutic option for the treatment of patients with chronic angina. Ranexa may be used with common cardiovascular medications, including beta-blockers, nitrates, calcium channel blockers, anti-platelet therapy, lipid-lowering therapy, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.[1]

Ranexa dosing is initiated at 500 mg twice daily and increased, based on clinical symptoms, to a maximum dose of 1000 mg twice daily. Tablets should be swallowed whole (do not crush, break or chew) and can be taken without regard to food. Ranexa is contraindicated in patients taking strong inhibitors of CYP3A (eg, ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir), taking inducers of CYP3A (eg, rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, and St. John's wort), and with clinically significant hepatic impairment.

With the revised labeling, the FDA removed a contraindication for use with moderate cytochrome P450 (CYP) 3A inhibitors. However the maximum dose of Ranexa should not exceed 500 mg twice daily when used with these medications (eg, diltiazem, verapamil, aprepitant, erythromycin, fluconazole, grapefruit juice, and grapefruit-containing products). The dose of Ranexa may need to be down-titrated, based on clinical response, when used in combination with inhibitors of P-glycoprotein (P-gp) such as cyclosporine. The dose of digoxin may need adjustment when used in combination with Ranexa. No dose adjustment of Ranexa is required in patients treated with CYP2D6 inhibitors, however lower doses of CYP2D6 substrates (eg, tricyclic antidepressants and antipsychotics) may be needed.

Although the mechanism of action for Ranexa's antianginal effects is not fully understood, Ranexa has antianginal and anti-ischemic effects that do not depend on reductions in heart rate or blood pressure. Ranexa does not affect the rate-pressure product, a measure of myocardial work, at maximal exercise. At therapeutic levels, Ranexa can inhibit the cardiac late sodium current (I_{Na}), however, the relationship of this inhibition to angina symptoms is uncertain. Ranexa blocks I_{Kr} and prolongs the QTc interval (mean 6 msec change with 1000 mg twice daily) in a dose-related manner. Clinical experience in an Acute Coronary Syndrome (ACS) population did not show increased risk of proarrhythmia or sudden death. Also in the recent labeling changes, the FDA removed a contraindication for use of Ranexa with QT-prolonging drugs. However, there is limited experience with high doses (> 1000 mg twice daily) or exposure, QT-prolonging drugs, or congenital potassium channel variants resulting in a long QT interval.

The expanded labeling for Ranexa is based on safety observations from a large ACS outcomes trial, MERLIN-TIMI 36 (N = 6,560). In this placebo-controlled trial, the primary endpoint was not met (P =.11) and therefore Ranexa is not indicated for the treatment of ACS. This trial did provide additional safety information and, in accordance with a protocol agreement between CVT and the FDA, it helped lead to the broader indication and new labeling for Ranexa, i.e. as an initial choice for the treatment of chronic angina. In this trial, ventricular arrhythmias were less common on ranolazine and there was no difference between Ranexa and placebo in the risk of all-cause mortality (relative risk ranolazine:placebo 0.99 with an upper 95% confidence limit of 1.22).

In controlled clinical trials of patients with angina, 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%). Additional effects of Ranexa include small reductions of hemoglobin A1c in patients with diabetes, the clinical significance of which is unknown. Ranexa should not be considered a treatment for diabetes.[1]

Please click here to see the package insert for Ranexa for full prescribing information. For additional information, please contact CV Therapeutics Professional Services at drug.info@cvt.com, or call 1-877-CVT-7171, option 2.

Sincerely,

Stephen L Harris, PharmD, Sr Director
Professional Services, Medical Affairs, CV Therapeutics, Inc.

Reference

1. Ranexa (ranolazine extended-release tablets) [package insert]; Palo Alto, CA: CV Therapeutics, Inc; November 2008.

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