Nonformulary Criteria for Use Checklist
Ranolazine
VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient. Individual cases that are outside the recommendations should be adjudicated at the local facility according to the policy and procedures of its P&T Committee and Pharmacy Services.

(For further details, refer to the drug monograph and update at www.pbm.va.gov or http://vaww.pbm.va.gov)

FDA APPROVED INDICATION FOR USE

Ranolazine is indicated in the treatment of chronic stable angina

EXCLUSION CRITERIA (If one is selected, patient is not eligible)

- ❑ Clinically significant hepatic impairment
- ❑ Receiving strong CYP 3A4 inhibitors including ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir.
- ❑ Receiving strong CYP 3A4 inducers including rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, or St. John's wort.

INCLUSION CRITERIA (Both must be selected to be eligible)

- ❑ Anginal episodes an average of 3 or more times per week despite maximal or maximally tolerated anti-anginal drug therapy (Defined as treatment with a beta-blocker, long-acting dihydropyridine calcium channel blocker and a long-acting nitrate).
- ❑ A VA healthcare provider is actively involved in the monitoring and management of ranolazine therapy and will re-assess ranolazine's therapeutic effectiveness and tolerability within 12 weeks after initiation of therapy.

PRECAUTIONS

- **QT-interval prolongation:** Ranolazine can prolong the QT interval in a dose-dependent manner. The mean increase (QTc) seen with 1000 mg twice daily was 6 milliseconds. There is little experience with ranolazine use in patients with pre-existing QT interval prolongation (Normal QTc <440 milliseconds). Use of ranolazine in these patients should be done with caution in the absence of safety data.
- **Drug-drug interactions:** Carefully review medications for possible drug-drug interactions prior to initiating ranolazine. Ranolazine is both an inhibitor of and a substrate for CYP 3A4 and P-glycoprotein and to a lesser extent CYP 2D6 (e.g., metoprolol). Dose adjustment of the object drug or avoidance of ranolazine may be recommended. There is little experience with ranolazine in combination with other drugs known to prolong the QT interval (e.g. Class Ia [quinidine] or Class III [amiodarone, dofetilide, sotalol] antiarrhythmics, erythromycin and some antipsychotic agents [thioridazine, ziprasidone]). Use of these drugs with ranolazine should be done with caution in the absence of safety data.

DOSAGE AND ADMINISTRATION

- Initiate therapy with 500 mg twice daily. Dose can be increased to a maximum of 1000 mg twice daily but dose escalation has not consistently been shown to improve symptoms. Adverse events with ranolazine are dose related.
- The maximum recommended dose of ranolazine should be limited to 500 mg twice daily in patients on concurrent therapy with moderate CYP3A inhibitors (e.g., diltiazem, verapamil, aprepitant, erythromycin, fluconazole, grapefruit-containing products).
- Down-titration of ranolazine dose based on clinical response may be needed when used concurrently with P-glycoprotein inhibitors such as cyclosporine.

ISSUES FOR CONSIDERATION

- Ranolazine prolongs the QT interval and has multiple drug interactions and precautions for use. It should be reserved for patients who have not received an adequate response with other antianginal drugs and should be used in combination with beta-blockers, nitrates and dihydropyridine (e.g. felodipine, amlodipine or long-acting forms of nifedipine) calcium channel blockers.
- Ranolazine was not shown to be pro-arrhythmic in a high risk ACS population.
- Ranolazine has been shown to increase drug levels of simvastatin by 2-fold. For most patients, this interaction is not expected to be clinically significant, and a dosing adjustment has not been recommended by the manufacturer or FDA. However, anecdotal reports within VA have noted adverse events potentially related to the combination, particularly due to elevated levels of simvastatin. Clinicians may wish to consider this issue when monitoring and counseling patients who are on both ranolazine and simvastatin.

RENEWAL CRITERIA (The following must be selected for renewal)

The therapeutic effectiveness and tolerability of ranolazine should be assessed within the first 12 weeks of ranolazine therapy:

- ❑ An improvement in anginal symptoms and/or a reduction in sublingual nitroglycerin consumption is documented in the medical record (while receiving ranolazine).
- ❑ Patient is not experiencing treatment-limiting adverse effects.