



Therapeutic Class ReviewSM

Ranolazine (RanexaTM)

July 2006

New Product for Review:

ranolazine (RanexaTM) [CV TherapeuticsTM]

Dossier Provided by Manufacturer: Yes

Dossier Evaluation: 1

- 1- dossier w/missing components
- 2- all components present, except pharmacoeconomic model
- 3- all components present (comprehensive)

Executive Summary

- Because of safety concerns, ranolazine (Ranexa) has FDA labeling only in patients who have inadequate response to other antianginal medications.
- Like other antianginal medications, ranolazine (Ranexa) does not modify the underlying disease process responsible for anginal pain (coronary artery disease).
- There are no studies with ranolazine (Ranexa) that evaluate clinical outcomes such as reduction in risk of myocardial infarction (MI), death, or improved patient survival.
- There are many generic/preferred options for treatment of chronic angina:
 - Beta-blockers (first-line)
 - Long-acting calcium channel blockers (first/second-line)
 - Long-acting nitrates (third-line).
- Risk of QT prolongation with ranolazine (Ranexa) is a potentially significant safety concern.
- The benefits of ranolazine (Ranexa) only outweigh the risk in patients whose symptoms are not controlled with other antianginal agents.

Evidence

- There is no useful evidence that ranolazine (Ranexa) provides clinically meaningful benefit in the treatment of chronic angina.
- Ranolazine (Ranexa):
 - Has no evidence of additional benefit over optimized antianginal medication therapy.
 - Has not been proven to be similar or superior to other antianginal treatment options.
 - Has not been studied in patients refractory to conventional antianginal therapies.
- Available harms information is not reliable for purposes of evaluating long-term safety of ranolazine (Ranexa).

- Preliminary safety concerns observed in clinical trials include a dose-related QT-prolongation and clinically significant drug interactions.

Decision

- Ranolazine (Ranexa) is non-preferred/non-formulary because:
 - There is no evidence that it is superior to alternative preferred antianginal medications.
 - There are safety concerns regarding its potential to cause QT-prolongation.

Products

Drug Products	FDA approval ^a	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^b
BETA-BLOCKERS				
atenolol (Tenormin [®]) ¹	8/1981	<ul style="list-style-type: none"> hypertension, angina pectoris due to coronary atherosclerosis, acute myocardial infarction. 	50 to 100 mg p.o. daily; for angina pectoris, may increase to 200 mg daily	arrhythmias, essential tremor, anxiety, congestive heart failure, gastro-intestinal bleeds, migraine prophylaxis, syncope, withdrawal symptoms
metoprolol (Lopressor [®]) ²	8/1978	<ul style="list-style-type: none"> hypertension, chronic angina pectoris, acute myocardial infarction. 	50 to 100 mg p.o. twice daily; may be dosed daily in hypertension; may increase to 400 mg/day in angina pectoris and 450 mg/day in hypertension	arrhythmias, essential tremor, anxiety, congestive heart failure, gastro-intestinal bleeds, migraine prophylaxis, syncope, withdrawal symptoms, aggressive behavior
nadolol (Corgard [®]) ³	12/1979	<ul style="list-style-type: none"> hypertension, chronic angina pectoris. 	Initial: 40 mg p.o. daily; increase in 40 to 80 mg increments; maximum dose for angina 160-240 mg/day and for hypertension 240-320 mg/day	arrhythmias, essential tremor, anxiety, gastro-intestinal bleeds, migraine prophylaxis, withdrawal symptoms, aggressive behavior, glaucoma
metoprolol ERT (Toprol-XL [®]) ⁴	1/1992	<ul style="list-style-type: none"> hypertension, chronic angina pectoris, heart failure. 	<ul style="list-style-type: none"> - 25 to 100 mg daily (max 400 mg/day) - 100 mg p.o. daily (max 400 mg daily) - 25 mg p.o. daily (max 200 mg/day) 	arrhythmias, essential tremor, anxiety, gastro-intestinal bleeds, migraine prophylaxis, syncope, withdrawal symptoms, aggressive behavior
CALCIUM CHANNEL BLOCKERS				
<i>dihydropyridines</i>				
amlodipine (Norvasc [®]) ⁵	7/1992	<ul style="list-style-type: none"> hypertension, chronic stable angina, vasospastic angina, angiographically documented coronary artery disease (CAD). 	5 to 10 mg p.o. daily	left ventricular hypertrophy, congestive heart failure (CHF), Raynaud's phenomenon, pulmonary hypertension, silent myocardial ischemia.
felodipine (Plendil [®]) ⁶	7/1991	<ul style="list-style-type: none"> hypertension. 	2.5 to 10 mg p.o. daily Angina: 2.5 to 5 mg p.o. twice daily.	chronic angina pectoris, cardiac dysrhythmia, congestive heart failure, Raynaud's phenomenon, chronic obstructive pulmonary disease (COPD).
nifedipine ERT (Procardia XL [®]) ⁷	9/1989	<ul style="list-style-type: none"> vasospastic angina, chronic angina, hypertension. 	30 to 60 mg p.o. daily; maximum: 90 mg/day	CHF, Raynaud's phenomenon, pulmonary hypertension, COPD, hiccoughs, migraine prevention, esophageal spasm.

<i>non-dihydropyridines</i>				
diltiazem ERT (Cardizem® CD) ⁸	6/1997	<ul style="list-style-type: none"> ▪ hypertension, ▪ chronic stable angina. 	<ul style="list-style-type: none"> - 180-240 mg daily; max: 540 mg/day - 120-180 mg daily; max: 480 mg/day 	cardiac dysrhythmia, CHF, hyperthyroidism, mania, migraine prevention, myocardial infarction, paroxysmal supra-ventricular tachycardia.
verapamil ERC (Isoptin® SR) ⁹	12/1986	<ul style="list-style-type: none"> ▪ essential hypertension ▪ angina pectoris 	<ul style="list-style-type: none"> - 240 mg p.o. daily; max: 480 mg daily - 180 mg p.o. daily; max: 540mg daily 	cardiac dysrhythmia, CHF, hyperthyroidism, mania, migraine prevention, myocardial infarction, paroxysmal supra-ventricular tachycardia.
NITRATES (LONG-ACTING)				
isosorbide dinitrate (Dilatrate® -SR) ¹⁰	9/1988	<ul style="list-style-type: none"> ▪ angina pectoris 	40 mg p.o. q 8-12 hours	achalasia, CHF, gastrointestinal bleed, myocardial infarction, pulmonary edema.
isosorbide mononitrate (Imdur®) ¹¹	8/1993	<ul style="list-style-type: none"> ▪ angina pectoris 	30 to 60 mg p.o. qAM; max: 240 mg daily	achalasia, CHF, gastrointestinal bleed, myocardial infarction, pulmonary edema.
METABOLIC MODULATOR				
ranolazine ERT (Ranexa™) ¹²	1/2006	<ul style="list-style-type: none"> ▪ chronic angina 	500-1000 mg p.o. BID	

^a Date applies to approval date for the original brand name medication where there are now generics available.

^b As listed in © 1974 - 2005 Thomson MICROMEDEX database or as referenced.

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