



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)

Available Therapeutic Alternatives for Treatment of Chronic Angina:

Preferred/Formulary	Non-preferred/non-formulary
BETA-BLOCKERS	
atenolol (Tenormin [®]) [generics]	
metoprolol (Lopressor [®]) [generics]	
metoprolol ERT (Toprol-XL [®]) [AstraZeneca]	
nadolol (Corgard [®]) [generics]	
CALCIUM CHANNEL BLOCKERS	
<i>dihydropyridines</i>	
felodipine (Plendil [®]) [generics]	amlodipine (Norvasc [®]) [Pfizer]
nifedipine ERT (Procardia XL [®]) [generics]	
<i>non-dihydropyridines</i>	
diltiazem ERC (Cardizem [®] CD) [generics]	
verapamil ERT (Isoptin [®] SR) [generics]	
NITRATES (LONG-ACTING)	
isosorbide dinitrate (Dilatrate [®] -SR) [generics]	
isosorbide mononitrate (Imdur [®]) [generics]	

Reason for Review

- To determine formulary status for ranolazine (RanexaTM), a new medication indicated for the treatment of chronic angina in patients who have not responded to conventional antianginal therapies.

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.

Considerations in subpopulations:

- *Pediatrics:* There is no useful evidence to establish the safety and efficacy in pediatric patients.
- *Geriatrics:* There were no overall differences in efficacy observed in younger versus older patients. About 48% of the subjects in clinical trials were ≥ 65 years of age. Patients ≥ 75 years of age appear to have a higher incidence of adverse events and discontinuations due to adverse events than younger subjects.
- *Race, ethnicity:* Current clinical experience has not identified differences in safety or efficacy based on race, or ethnicity.
- *Gender:* There is insufficient evidence to establish the benefit of ranolazine (Ranexa) in women.

Conclusion

- 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	Cost ^b	Potential Off-label Uses ^c
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	\$1.50 to \$3.60	arrhythmias, essential tremor, anxiety, congestive heart failure, gastrointestinal 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	\$0.90 to \$1.50	arrhythmias, essential tremor, anxiety, congestive heart failure, gastrointestinal 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	\$15 to \$30	arrhythmias, essential tremor, anxiety, gastrointestinal 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) 	\$44 to \$175	arrhythmias, essential tremor, anxiety, gastrointestinal 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	\$54 to \$74	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.	\$29 to \$51	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	\$28 to \$62	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 	\$26 to \$81	cardiac dysrhythmia, CHF, hyperthyroidism, mania, migraine prevention, myocardial infarction, paroxysmal supraventricular 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 	\$18 to \$54	cardiac dysrhythmia, CHF, hyperthyroidism, mania, migraine prevention, myocardial infarction, paroxysmal supraventricular tachycardia.

Drug Products	FDA approval ^a	FDA approved indications	Usual Dose/Route	Cost ^b	Potential Off-label Uses ^c
NITRATES (LONG-ACTING)					
isosorbide dinitrate (Dilatrate [®] -SR) ¹⁰	9/1988	▪ angina pectoris	40 mg p.o. q 8-12 hours	\$29 to \$44	achalasia, CHF, gastrointestinal bleed, myocardial infarction, pulmonary edema.
isosorbide mononitrate (Imdur [®]) ¹¹	8/1993	▪ angina pectoris	30 to 60 mg p.o. qAM; max: 240 mg daily	\$7 to \$9	achalasia, CHF, gastrointestinal bleed, myocardial infarction, pulmonary edema.
METABOLIC MODULATOR					
ranolazine ERT (Ranexa [™]) ¹²	1/2006	▪ chronic angina	500-1000 mg p.o. BID	\$207 to \$413	

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

^b Cost estimate based on AWP (average wholesale price) listed in First Data Bank or MAC (maximum allowable cost) as of April 2006 for 30 days of therapy.

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

References

1. Tenormin[®] (atenolol) Prescribing Information. AstraZeneca Pharmaceuticals LP: Wilmington, DE, February 2005.
2. Lopressor[®] (metoprolol tartrate) Prescribing Information. Novartis Pharmaceuticals Corporation: East Hanover, NJ, November 2004.
3. Corgard[®] (nadolol) Prescribing Information. Bristol-Myers Squibb Company: Princeton, NJ, October 2001.
4. Toprol-XL[®] (metoprolol succinate extended-release) Prescribing Information. AstraZeneca Pharmaceuticals LP: Wilmington, DE, February 2005.
5. Norvasc[®] (amlodipine besylate) Prescribing Information. Pfizer Inc.: New York, NY, September 2005.
6. Plendil[®] (felodipine extended-release) Prescribing Information. AstraZeneca Pharmaceuticals LP: Wilmington, DE, November 2003.
7. Procardia XL[®] (nifedipine extended-release) Prescribing Information. Pfizer Inc.: New York, NY, August 2003.
8. Cardizem[®] CD (diltiazem HCl) Prescribing Information. Biovail Pharmaceuticals, Inc.: Morrisville, NC, August 2001.
9. Isoptin[®] SR (verapamil sustained-release) Prescribing Information. Knoll Pharmaceutical Company: Mt. Olive, NJ.
10. Dilatrate[®]-SR (isosorbide dinitrate sustained-release) Prescribing Information. Schwarz Pharma: Milwaukee, WI, September 2003.
11. Imdur[®] (isosorbide mononitrate extended-release) Prescribing Information. Key Pharmaceuticals, Inc.: Kenilworth, NJ, July 2002.
12. Ranexa[™] (ranolazine extended-release) Prescribing Information. CV Therapeutics, Inc.: Palo Alto, CA, February 2006.
13. Chaitman BR, Pepine CJ, Parker JO, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina [CARISA]. JAMA. 2004;291:309-16.
14. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina [MARISA]. J Am Coll Cardiol. 2004;43(8):1375-82.
15. Stone PH, Gratsiansky NA, Blokhin A, et al. Antianginal efficacy of ranolazine when added to maximal treatment with conventional therapy: the efficacy of ranolazine in chronic angina [ERICA] trial. Circulation. 2005;112(17);Abstract 3491.
16. Center for Drug Evaluation and Research. Approval package for application number NDA 21-526; Medical Review. Available at: http://www.fda.gov/cder/foi/nda/2006/021526_s000_Ranexa.htm.
17. Cocco G, Rousseau MF, Bouvy T, et al. Effects of a new metabolic modulator, ranolazine, on exercise tolerance in angina pectoris patients treated with beta-blocker of diltiazem. J Cardiovasc Pharmacol. 1992;20(1):131-8.
18. Rousseau MF, Pouleur H, Cocco G, et al. Comparative efficacy of ranolazine versus atenolol for chronic angina pectoris. Am J Cardiol. 2005;95(3):311-16.

19. Pepine CJ, Wolff AA. A controlled trial with a novel anti-ischemic agent, ranolazine, in chronic stable angina pectoris that is responsive to conventional antianginal agents. *Am J Cardiol.* 1999;84(1):46-50.
20. Thadani U, Ezekowitz M, Fenney L, et al. Double-blind efficacy and safety study of a novel anti-ischemic agent, ranolazine, versus placebo in patients with chronic stable angina pectoris. *Circulation.* 1994;90(2):726-34.
21. Ciapponi A, Pizarro R, Harrison J. Trimetazidine for stable angina. *The Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No.: CD003614.pub2. DOI: 10.1002/14651858.CD003614.pub2.
22. O'Toole L. Angina (stable) [search date December 2004]. *Clin Evid.* 2005;14:1-7.
23. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for the Management of Patients with Chronic Stable Angina). 2002. Available at: www.acc.org/clinical/guidelines/stable/stable.pdf.
24. Scottish Intercollegiate Guidelines Network (SIGN). Management of Stable Angina: A national clinical guideline. April 2001. Available at: <http://www.sign.ac.uk/pdf/sign51.pdf>.
25. Product Dossier: Ranexa (ranolazine extended-release tablets). CV Therapeutics: Palo Alto, CA. Reviewed 4/10/06.
26. Hill J, Timmis A. ABC of clinical electrocardiography: Exercise tolerance testing. *BMJ* 2002;324: 1084-7.
27. American Heart Association [homepage] ©2006. Diagnosing heart disease; New York Heart Association (NYHA) functional classification. Available at: <http://www.americanheart.org/presenter.jhtml?identifier=330#most>. Accessed on 4/17/06.
28. Kimble LP, Dunbar SB, Weintraub WS, et al. The Seattle Angina Questionnaire: reliability and validity in women with chronic stable angina. *Hear Dis.* 2002;4:206-11.
29. Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol.* 1995;25:333-41.