CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-526/S004

OTHER REVIEW(S)

RHPM Overview of NDA 21-526 S-004
Ranexa (ranolazine) 500 and 1000 mg Extended-Release (ER) Tablets
November 6, 2008

Sponsor:	CV Therapeutics
Supplement Type:	SE-1
Receipt Date:	September 27, 2007
User Fee Goal Date:	July 27, 2008
Letter Issued:	November 5, 2008
Final Draft Labeling:	November 5, 2008

Background
The sponsor submitted NDA 21-526 for Ranexa (ranolazine) 500 mg and 1000 mg extended release (ER) tablets, which were approved for the treatment of chronic angina in a restricted population on 27 January 2006 and 12 February 2007, respectively. CV Therapeutics, Inc.

The sponsor submitted this Prior Approval Supplement [redacted] (b) (4) 004, [redacted] (b) (4) (reviewed in DMEP) with clinical data to support the use of Ranexa as first-line therapy for the long-term treatment of chronic angina (S-004) [redacted] (b) (4)

The sponsor referenced July 27, 2004 Special Protocol Assessment (SPA) agreement under IND 43,735 for Study CVT 3036 (MERLIN TIMI-36), entitled "A Randomized, Double-blind, Parallel-group, Placebo-controlled, Multi-national Clinical Trial to Evaluate the Efficacy and Safety of Ranolazine versus Placebo in Patients with Non-ST Segment Elevation Acute Coronary Syndrome." and the Pre-NDA Meeting with the Division on June 27, 2007.

The supplement has primary reviews by Dr. Lee (DMEP, 11 April 2008), Ms Masucci (SEALD, 19 June 2008), Cdr. Hubbard (DDMAC, 10 March 2008), Drs. Hinderling and Mehrotra (clinical pharmacology and pharmacometrics; 28 May 2008) and Drs. Gordon and Friedlin (medical and statistical; 21 April 2008). Dr. Gordon has also reviewed numerous amendments that the sponsor files in response to the Division's comments (22 September; 24 September (2); 26 September (2); 20 October (2). There are two CDTL memos by Dr.Marciniak (21 July 2008; 23 October 2008).

Office Director's Memorandum
N/A

Division Director's Memorandum
Dr. Stockbridge noted in his Division Director's Memo dated November 1, 2008 supports approval of S-004 for the removal of the second-line restriction on the use of ranolazine to treat patients with chronic stable angina.

CDTL Review
Dr. Marciniak noted in his CDTL Memo dated October 23, 2008 he recommended that ranolazine is recommended for approval of ranolazine for the treatment of chronic angina. The major study submitted, CVT 3036, provides reassurance that ranolazine is safe at the marketed dosage in high risk ACS patients without potential drug interactions. The results in the subgroup treated with ranolazine and diltiazem or verapamil do not confirm that ranolazine at full dosage is safe in this subgroup, one with a known yet moderate drug interaction. I recommend that ranolazine dosage be cut in half for patients taking diltiazem, verapamil or other moderately strong CYP3A4 or Pgp inhibitors. Ranolazine appears to have the potential for many drug interactions that are not well characterized but also, except for the

interaction with diltiazem and verapamil, do not appear dangerous. He also recommended postmarketing safety studies as outline below under Postmarketing studies.

(b) (4)

Medical Review
In her review dated April 21, 2008, Dr. Gordon concluded that Protocol CVT 3036 enrolled a total of 6556 subjects who were hospitalized for non-ST elevation acute coronary syndrome (ACS) with the qualifying event being at least one episode of ischemic symptoms at rest. Subjects were randomized to either ranolazine or placebo and followed for at least 8 months.

The primary efficacy endpoint was a composite of cardiovascular (CV) death, MI, and recurrent ischemia. The primary efficacy analysis was time from randomization to first occurrence of CV death, myocardial infarction (MI), or recurrent ischemia. The null hypothesis was that there is no difference between the study treatments with respect to the time to first occurrence of any element of the primary efficacy endpoint. Key results: There were 1448 subjects who experience a primary efficacy event. The null hypothesis was not rejected. There was no statistical difference between the treatment groups for the composite endpoint (p=0.11). The incidence of death from any cause was approximately 5.3% for both treatment groups. The relative risk of mortality (ranolazine: placebo) was 0.988 (95% CI 0.80, 1.21). Therefore, a 21% or greater increase in mortality resulting from ranolazine use can be excluded with 95% confidence. The percents of those deaths deemed to be sudden were also similar for the two treatment groups (2% for placebo and 1.7% for ranolazine). Based on the findings of this medium sized study, ranolazine, compared to placebo and within certain limits, does not increase mortality, the occurrence of MIs, or recurrent ischemia in subjects with non-ST elevation ACS. It is reasonable to allow the promotion of ranolazine as a first-line treatment for chronic stable angina.

Conclusions from the 6 additional trials are:
-The addition of diltiazem 180 mg bid increases ranolazine AUC0-12 by more than 2 fold (CVT 301-19);
-many subjects are unable to tolerate doses 1500 mg bid and above. Dose limiting adverse events include syncope, nausea, dizziness, and vomiting (CVT 3023);
-no unexpected adverse events were reported in the uncontrolled safety trials (CVT 3024, 3032, 3034).
Study CVT 3036, the clinical outcome trial, is discussed in detail in this review. The other studies are briefly presented.

Please also see amended reviews dated 10/20/08 (2), 9/26/08 (2), 9/24/08 (2), 9/22/08.

Refer to the financial disclosure is a dated June 6, 2008.

Pharmacology Review
N/A

Chemistry Review
In his review dated June 25, 2008, Dr. Chidambaram noted that this drug is currently approved for the treatment of chronic angina. This application is submitted to seek approval for first line therapy for the long-term treatment of chronic angina. No new CMC information was submitted in this application. Minor changes are proposed to the "Description" and "How Supplied" sections of labeling. The reviewer recommended the following changes to "Description" section of labeling: Ranexa (ranolazine) is available as a film coated, extended-release tablet for oral administration.

The applicant submitted a claim for categorical exclusion under 21 CFR 25.31 (b). Based on applicant's calculation for the expanded indication and also based on production volume of drug substance, the amount of active moiety that is expected to enter into the aquatic environment is slightly greater than 1 ppb. However, the applicant has further indicated that based on metabolism and excretion of pharmacologically active ingredient, the actual amount of pharmacologically active material with potential for environmental impact would be approximately (b) (4). Owing to the above difference in EIC, a consult to evaluate the EA document was sent to OPS. Dr. Raanan Bloom in an e-mail dated 06/06/2008 indicated his acceptance of applicant's calculation accounting for metabolites and their claim under 21 CFR 25.31 (b). Based on the above, the applicant's claim is found to be acceptable.

Statistical Review

(b) (4)

Biopharmaceutical Review
Refer to Dr. Hinderling of the Office of Clinical Pharmacology review dated May 28, 2008 in which he noted that S-004 is acceptable from a Clinical Pharmacology view point.

DSI
No Division of Scientific Investigation was recommended for this application.

Pediatric Rule
N/A

Labeling
The labeling for this sNDA is attached to the approval letter. Also, see the labeling recommendations in the Clinical, SEALD and CDTL reviews.

Advisory Committee Meeting
This application did not go before the Advisory Committee.

Project Manager's Summary
To my knowledge, there are no issues that might prevent taking regulatory action on this NDA.

John David, BSN, MS in HRM
Regulatory Health Project Manager

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John David
11/6/2008 10:31:23 AM
CSO

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 21-526 (Ranexa; ranolazine for angina)

Sponsor: CV Therapeutics

Review date: 1 November 2008

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 21-526
HFD-110/Project Manager

This memo conveys the Division's recommendation to remove the second-line restriction on the use of ranolazine to treat patients with chronic stable angina.

Supplement 004 was submitted 27 September 2007 and the PDUFA goal date is 27 July 2008. The supplement has primary reviews by Dr. Lee (DMEP, 11 April 2008), Ms. Masucci (SEALD, 19 June 2008), Cdr. Hubbard (DDMAC, 10 March 2008), Drs. Hinderling and Mehrotra (clinical pharmacology and pharmacometrics; 28 May 2008) and Drs. Gordon and Friedlin (medical and statistical; 21 April 2008). Dr. Gordon has also reviewed numerous amendments that the sponsor files in response to the Division's comments (22 September; 24 September (2); 26 September (2); 20 October (2). There are two CDTL memos by Dr.Marciniak (21 July 2008; 23 October 2008).

The main basis for (b) (4) claims made is study CVT 3036 or MERLIN-TIMI 36. This was a double-blind, placebo-controlled, international study conducted in patients within 48 hours of onset of acute coronary syndrome. Subjects were on a background of platelet inhibitors, ACE inhibitors, beta blockers, statins, etc. Ranolazine was administered first IV (up to 4 days) at a level predicted to achieve plasma levels similar to what is seen with chronic oral dosing. The primary end point was time to first event of cardiovascular death, MI, or recurrent ischemia (RI), to be analyzed using intent-to-treat with alpha=0.05. Study power was set by enrollment to 730 CV end point events and 310 all-cause deaths. Secondary end points, to be analyzed in sequence, were (a) CV death, MI, and severe RI, (b) CV death, MI, RI, ischemia by Holter, hospitalization for CHF, or positive ETT, (c) CV death, MI, severe RI, or ischemia by Holter within 30 days, (d) angina frequency by Seattle Angina Questionnaire, (e) physical limitation by SAQ, (f) ETT at 8 months, and (g) ischemia by Holter over the first 72 hours.

Study follow-up was about a year, but about 25% of patients discontinued treatment (similar rates in both groups), about half for "withdrawal of consent". This high withdrawal rate limits the study's utility to support its primary aim.

Although it leans favorably, there was no statistically significant effect on the primary end point (RR=0.92; p=0.11), and the sponsor makes no claim for use in the ACS population. There was about a 15% reduction the most common event (recurrent ischemia), but about a 10% higher incidence of cardiovascular death. Although the latter was not statistically significant and all-cause mortality about the same, this inconsistency in end point components probably would have been difficult to accept, had the study been successful overall. Among the secondaries, angina frequency was reduced (p<0.001), but the others showed no nominal statistical significance (p-values from 0.05 to 0.91).

(b) (4)

(b) (4)

In the remainder of this memo, I address safety issues raised in Dr. Marciniak's memos, and I refer to the latter memo and the sponsor's various amendments addressing these concerns.

A considerable effort went into exploring an adverse trend in some safety parameters in subjects who were on the combination of ranolazine and either diltiazem or verapamil. Diltiazem and verapamil are moderate CYP3A inhibitors that result in roughly doubling the exposure to ranolazine, when the highest recommended dose of ranolazine (1000 mg BID) is already at the limits of tolerability. Thus some safety signal would not be unexpected with the use of these drugs in combination with Ranexa.

Good records on concomitant medications were kept only during the index hospitalization. Start and stop dates for concomitant medications are generally unavailable for the post-hospitalization period.

Adverse events by use of diltiazem or verapamil[1]

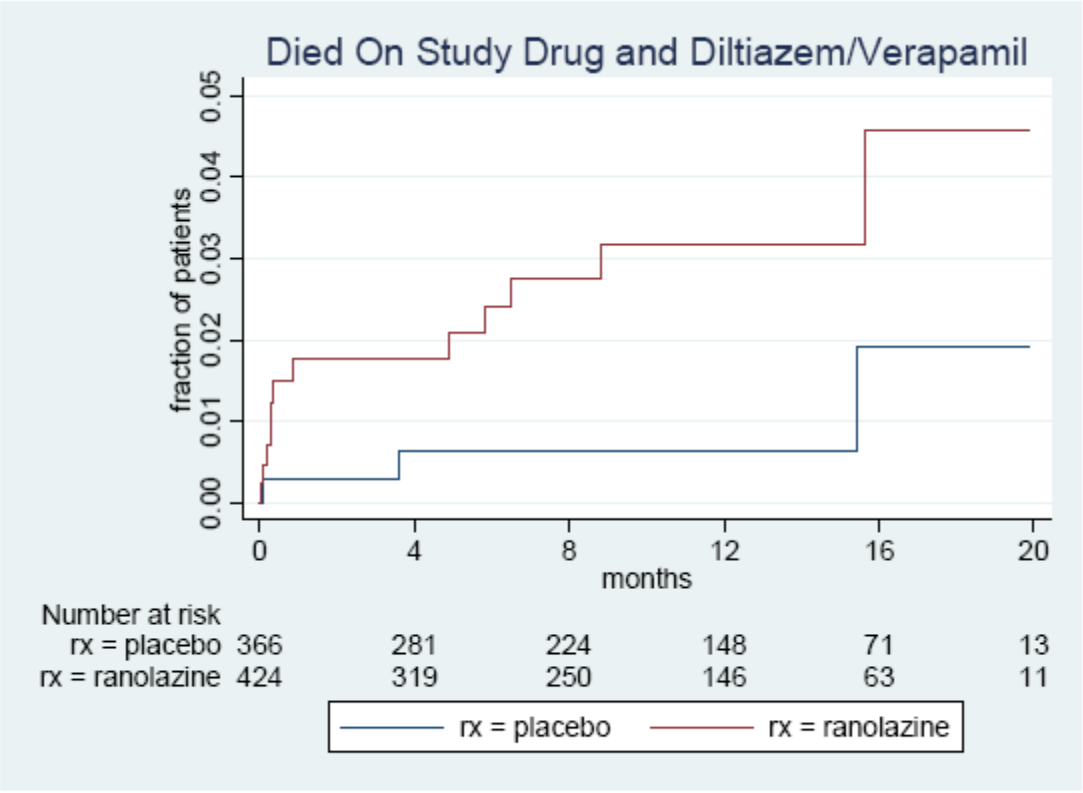
	Dizziness Post-hosp Dilt/Verap		**Asthenia Post-hosp Dilt/Verap**		**SAEs Post-hosp Dilt/Verap**		**AE Withdrawals Post-hosp Dilt/Verap**		**Deaths In-hosp Dilt/Verap**		**Deaths Post-hosp Dilt/Verap**	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Raw												
Plac	7%	10%	3%	3%	33%	44%	7%	11%	1.3%	1.3%	4.2%	3.2%
Ran	13%	22%	5%	8%	32%	52%	13%	16%	1.4%	2.3%	3.7%	6.0%
Corr[2]												
Plac	--	3%	--	0%	--	11%	--	4%	--	0%	--	-1.0%
Ran	6%	15%	2%	5%	-1%	19%	6%	9%	0.1%	1.0%	-0.5%	1.8%

[1] *Data from Dr. Marciniak's memo*

[2] *My placebo-subtraction based on raw rounded percentages shown.*

By Dr. Marcinak's analyses, none of the ranolazine-diltizam/verapamil interactions is statistically significant, but for each comparison, there are more events on the combination than expected based on the summed contributions of the individual treatments of ranolazine or diltiazem/verapamil.

Dr. Marciniak's log-rank analysis (shown below) of all-cause mortality among subjects on diltiazem or verapamil gives a nominally statistically significant difference (p=0.035) for ranolazine being worse than placebo.



p = 0.035 by log rank

Dr. Marciniak shows some of these analyses (dizziness, AE withdrawals post-hospitalization, deaths in-hospital, and deaths post-hospitalization) for subjects on or off amlodipine, again without denominators, and there is less of a sign of an adverse interaction (for only withdrawals for AEs was use together associated with more events than the sum of the rates on ranolazine or amlodipine alone).

The sponsor adds a number of observations that are not addressed by Dr. Marciniak.

1. The sponsor notes evidence that among subjects taking diltiazem, the subjects randomized to ranolazine were somewhat older, had a higher history of MI, angina, unstable angina, heart failure, cerebrovascular disease, and resuscitated sudden death. Somewhat fewer ranolazine subjects were on lipid-lowering drugs, beta-blockers, and ACE inhibitors, and somewhat more were on nitrates, hypoglycemics, and antiarrhythmics.

2. At my request, the sponsor (submission of 31 July 2008) took a more systematic look at mortality in the pooled diltiazem/verapamil cohort. They looked at all-cause, cardiovascular, and sudden cardiac deaths in this cohort, censoring at the time of the last dose, 7 days after the last dose, 30 days after the last dose, or using all data to the

end of the study. They did a similar set of analyses on subjects not receiving diltiazem or verapamil. These analyses are summarized below:

Deaths by use of CCBs and censoring time

	On Ver or Dilt				**Never on Ver or Dilt**			
	PLC N=308		**RAN N=349**		**PLC N=2965**		**RAN N=2918**	
	Events		**RR**	**P**	**Events**		**RR**	**P**
	PLC	**RAN**			**PLC**	**RAN**		
All-cause								
To last dose	15	14	1.00	0.98	160	102	0.75	0.025
+ 7 days	15	14	0.99	0.98	160	111	0.81	0.08
+30 days	15	16	1.11	0.78	160	123	0.88	0.27
All available	15	23	1.37	0.34	160	149	0.95	0.64
Cardiovascular								
To last dose	13	13	1.09	0.84	135	96	0.83	0.17
+ 7 days	13	13	1.07	0.87	135	103	0.88	0.33
+30 days	13	15	1.20	0.63	135	112	0.94	0.61
All available	13	20	1.37	0.37	135	127	0.96	0.73
Sudden								
To last dose	4	6	1.77	0.37	61	43	0.84	0.38
+ 7 days	4	6	1.74	0.39	61	43	0.83	0.35
+30 days	4	6	1.69	0.42	61	45	0.85	0.41
All available	4	7	1.57	0.47	61	49	0.82	0.29

Thus, really no hint of an increase in the risk of all-cause mortality appears until one includes subjects who were off study drug for more than 30 days at the time of the event. Even with that, the sign of harm is less strong than is the sign that ranolazine is life-preserving in subjects not on diltiazem or verapamil.

3. At my request, the sponsor looked at interactions based on concomitant use of other CYP3A or P-gp inhibitors. This list is enriched in antibiotics and other therapy less likely to have been chronically administered than was diltiazem or verapamil. Thus, the analysis is not too useful as a test of effects of CYP 3A inhibition as it is instructive regarding the power to generate effects that are likely to be spurious.

There were 135 subjects on placebo and 138 on Ranexa who, at some point received, concomitant CYP 3A or P-gp inhibitors other than diltiazem and verapamil. In these cohorts, there were 23 deaths on placebo and 7 deaths on Ranexa, the corresponding 360-day K-M estimated death rates being 14.7% on placebo and 5.3% on Ranexa, about a 64% risk *reduction*, much larger than the nominal risk *increase* associated with diltiazem or verapamil. In this group, adverse events resulting in withdrawal were more common on ranolazine (23% vs. 15%, about the same difference as in the population never receiving a CYP 3A or P-gp inhibitor), and SAEs were slightly less common on ranolazine (54% vs. 57%, exactly matching the difference in the population never receiving CYP 3A or P-gp inhibitors).

I conclude that, while I cannot rule out any possibility of harm associated with use of diltiazem or verapamil, what sign of harm that appears here is small, and likely to be either the play of chance or attributable to baseline differences between the subjects randomized to placebo or ranolazine in this cohort.

Poor tolerability of a high dose of ranolazine plus dilatiazem or verapamil is more clear and more likely. I concur on the dose reduction recommendation for this setting. Use of ranolazine with strong CYP 3A inhibitors should remain contraindicated.

Dr. Marciniak looked for potential adverse interactions with statins on dizziness, myalgia, hepatic adverse events, adverse events leading to withdrawal, deaths, changes in LDL, and changes in ALT. He concludes that no clinically important interaction was evident, and I concur.

(b) (4)

Dr. Marciniak notes some cases of leucopenia, pancytopenia, and thrombocytopenia; these terms need to be added to the list of rare adverse events.

There were more cancers reported on ranolazine than on placebo, with Dr. Marciniak's K-M curves looking different mostly because there were no placebo cases reported after 11 months. I agree with his assessment that this is not particularly worrisome.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge
11/3/2008 10:51:02 AM
MEDICAL OFFICER

MEMORANDUM

To: **John David**
Division of Cardiovascular and Renal Products

From: **Iris Masucci, PharmD, BCPS**
for Study Endpoints and Label Development (SEALD) Team, OND

Date: **June 12, 2008**

Re: **Comments on draft labeling for Ranexa (ranolazine)**
NDA 21-526/S-004

We have reviewed the proposed label for Ranexa (FDA version received 6/9/08) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the Division after a full review of the submitted data.

Please see attached label for recommended changes.

28 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Iris Masucci
6/19/2008 02:45:24 PM
DDMAC REVIEWER

Laurie Burke
6/19/2008 05:40:22 PM
INTERDISCIPLINARY

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 10, 2008
To:	Norman Stockbridge, MD, Ph.D, Director Division of Cardiovascular and Renal Products Mary Parks, MD, Director Division of Metabolism and Endocrine Products
Thru:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention
From:	Jinhee J. Lee, PharmD, Safety Evaluator Division of Medication Error Prevention
Subject:	Insert Labeling Review
Drug Name:	Ranexa (ranolazine) Extended-release Tablets 500 mg, 1000 mg
Application Type/Number:	NDA 21-526, S-004/(b) (4) (b) (4)
Applicant:	CV Therapeutics
OSE RCM #:	2007-2504

1 INTRODUCTION

This review was written in response to a request from the Division of Cardiovascular and Renal Products to review the labeling supplements for NDA 21-526 (S-004 (b) (4) (b) (4) for Ranexa. The applicant has submitted applications to expand the existing indication to first-line therapy for the long-term treatment of chronic angina. (b) (4)

1.1 REGULATORY HISTORY

Ranexa was approved on January 27, 2006 with the indication for treatment of chronic angina. Ranexa is currently approved for patients who have not achieved an adequate response with other anti-anginal drugs because Ranexa was shown to prolong the QT interval. The applicant has now submitted an application to include one revised indication (b) (4)

1.2 PRODUCT INFORMATION

Ranexa (ranolazine) has anti-ischemic and antianginal effects that do not depend upon reductions in heart rate or blood pressure in coronary artery disease patients. (b) (4)

Ranexa was previously indicated for the 2nd line treatment of chronic angina. However, the applicant now proposes to expand this indication to first-line therapy for the long-term treatment of chronic angina, (b) (4)

The recommended dose for the treatment of chronic angina is 500 mg to 1000 mg twice daily, as needed, based on clinical symptoms. Ranexa may be taken with or without meals and should be swallowed whole and not crushed, broken, or chewed. The project manager for the Division of Cardiovascular and Renal Products informed us that the dosage is the same for all (b) (4) indications.

Ranexa is supplied as 500 mg and 1000 mg tablets in 60 tablet unit-of-use bottles and 500 tablet pharmacy bottles.

2 MATERIAL REVIEWED

For this product the applicant submitted on September 27, 2007 revised prescribing information for the Division of Medication Error Prevention review. The Division of Medication Error Prevention compared the revised labeling to both the current and previously approved labeling to identify any areas of concern from a medication errors perspective.

3 DISCUSSION

After reviewing the prescribing information, the Division of Medication Error Prevention notes that the applicant has not included the information pertaining to their expanded indications in the appropriate places (i.e. Indications and Usage, Dosage and Administration). Instead, it appears that information relating to these new indications have been included in section 8 (Use in Specific Populations) and section 14 (Clinical Studies). In an internal meeting with the Division of

Cardiovascular and Renal Products on April 8, 2008, the Division agreed that there were problems with the insert labeling and that they planned on revising the insert labeling extensively.

4 CONCLUSIONS AND RECOMMENDATIONS

We note that many of the issues we have regarding the insert labeling relate to the (b) (4)

Thus, the Division of Medication Error Prevention would like to actively participate in the labeling discussion while the insert labeling is being reviewed. We look forward to meeting with the Division for further discussion when appropriate. If you have further questions or need clarifications, please contact Darrell Jenkins, OSE Project Manager, at 301-796-0558.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jinhee Jahng
4/10/2008 03:16:48 PM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
4/10/2008 03:18:46 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/11/2008 02:51:05 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

To: CDR John David
Division of Cardiovascular and Renal Products

From: Lisa Hubbard, R.Ph.
Senior Regulatory Review Officer
DDMAC, HFD-42

Date: March 10, 2008

Re: Comments on draft labeling:
NDA 21-526
Ranexa™ (ranolazine) Tablets

DDMAC has reviewed the proposed package insert (PI) for NDA 21-526, Ranexa™ (ranolazine) and offers the following comments with regard to promotional considerations. This review is based on the proposed PI submitted to the EDR, and concerns only promotional considerations associated with the proposed PI.

(b) (4)

[redacted]


(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lisa Hubbard
3/10/2008 03:47:28 PM
DDMAC REVIEWER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-526 Supplement # 004 (SE 1) (b) (4) Efficacy Supplement Type SE-

Proprietary Name: Ranexa
Established Name: ranolazine
Strengths: 500 and 1000 mg Extended-Release (ER) Tablets

Applicant: CV Therapeutics
Agent for Applicant (if applicable):

Date of Application: September 27, 2007
Date of Receipt: September 27, 2007
Date clock started after UN:
Date of Filing Meeting: November 7, 2007
Filing Date: November 27, 2007
Action Goal Date (optional): July 27, 2008 User Fee Goal Date: July 27, 2008

Indication(s) requested: 1) S-004: first-line therapy for the long-term treatment of chronic angina. (b) (4)

Type of Original NDA: (b)(1) ☐ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☒ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.*

Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☒

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☒

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

  1. This application is a paper NDA YES ☐

  2. This application is an eNDA or combined paper + eNDA YES ☐
     This application is: All electronic ☒ Combined paper + eNDA ☐
     This application is in: NDA format ☐ CTD format ☐
     Combined NDA and CTD formats ☒

     Does the eNDA, follow the guidance?
     (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

     If an eNDA, all forms and certifications must be in paper and require a signature.

     If combined paper + eNDA, which parts of the application were submitted in electronic format?

     Additional comments:

  3. This application is an eCTD NDA. YES ☒

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES ☐ NO ☒

***10/12/05 letter fully waived peds. study. Langauge will be sent to peds team.

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO ☒

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: **43,735**

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒

If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 6/27/07 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) 7/24/04 NO ☐
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☒ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐

If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☐
- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☒

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11/7/07

NDA #: 21-526

DRUG NAMES: Ranexa (ranolazine) 500 and 1000 mg Extended-Release (ER) Tablets

APPLICANT: CV Therapeutics

BACKGROUND: The sponsor submitted NDA 21-526 for Ranexa (ranolazine) 500 mg and 1000 mg extended release (ER) tablets, which were approved for the treatment of chronic angina in a restricted population on 27 January 2006 and 12 February 2007, respectively. CV Therapeutics, Inc.

The sponsor submitted this Prior Approval Supplement [redacted (b) (4)] 004, [redacted (b) (4)] (reviewed in DMEP) with clinical data to support the use of Ranexa as first-line therapy for the long-term treatment of chronic angina (S-004) [redacted (b) (4)]

The sponsor referenced July 27, 2004 Special Protocol Assessment (SPA) agreement under IND 43,735 for Study CVT 3036 (MERLIN TIMI-36), entitled "A Randomized, Double-blind, Parallel-group, Placebo-controlled, Multi-national Clinical Trial to Evaluate the Efficacy and Safety of Ranolazine versus Placebo in Patients with Non-ST Segment Elevation Acute Coronary Syndrome." and the Pre-NDA Meeting with the Division on June 27, 2007.

ATTENDEES:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Maryann Gordon, M.D.	Medical Officer, HFD-110
Valerie Freidlin, Ph.D.	Statistician, HFD-710
Nallaperum Chidambaram, Ph.D.	Chemistry Pharmaceutical Assessment Lead, ONDQA
Peter Hinderling, M.D.	Clinical Pharmacology, HFD-860
John David	Regulatory Health Project Manager, HFD-110
Haley Seymour	DMEP
Sally Choe	DMEP
Johnny Lau	DMEP
Jon Sahlroot	DMEP
Robert Mishbin	DMEP
Janice Derr	

ASSIGNED REVIEWERS (including those not present at filing meeting):

Discipline/Organization	**Reviewer**	**Review Goal Dates**
Medical:	Gordon	5/27/07
Secondary Medical:		
Statistical:	Freidlin	5/27/07
Pharmacology:		
Statistical Pharmacology:		
Chemistry:	Chidambaram	5/27/07
Environmental Assessment (if needed):		
Biopharmaceutical:	Hinderling	5/27/07
Microbiology, sterility:		
Microbiology, clinical (for antimicrobial products only):		
DSI:	N/A	
OPS:		
Regulatory Project Management:	David	
Other Consults:	DMETS DDMAC	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☐ NO ☒
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☒
  YES

PHARMACOLOGY/TOX N/A ☒ FILE ☐ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Sterile product? YES ☐ NO ☒
  If yes, was microbiology consulted for validation of sterilization?

YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

☐ No filing issues have been identified.

☒ Filing issues to be communicated by Day 74. List (optional):

CVT 3119
Please provide a full study report.

CVT 3032
Please summarize the plasma concentration data ordered for dose and time of measurement and provide appropriate plots and descriptive statistics.

CVT 3114
1. The report does not indicate whether the reader of the echo-cardiograms was blinded.
2. A plot of the Fridericia corrected QTc on RR (in the absence of drug) could not be found.
3. The description about the hierarchy of the leads used to determine QT and RR intervals is not clear. Was Lead II used as default to determine QT and Leads V5 or V3 only when the QT interval could not be determined from Lead II or was QT determined as the average from Leads II, V5 and V3?

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

John David
Regulatory Project Manager

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John David
12/3/2007 01:57:46 PM
CSO