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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-526

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-526

CV Therapeutics, Inc.
Attention: Ms. Carol Karp
Vice President, Regulatory Affairs
3172 Porter Drive
Palo Alto, CA 94304

Dear Ms. Karp:

Please refer to your new drug application (NDA) originally submitted December 27, 2002, and resubmitted July 26, 2005, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ranexa (ranolazine) 500 mg Extended-Release Tablets.

We acknowledge receipt of your submissions dated August 1 and 15, September 15, October 5, 6, 7 (two), 10, 14, 17, 19, and 27, November 21 and 30, December 2, 6, 14, and 15, 2005, and January 5, 6, and 19, 2006.

Your July 26, 2005 submission constituted a complete response to our October 30, 2003 approvable letter.

This new drug application provides for the use of Ranexa (ranolazine) 500 mg Extended-Release Tablets for the treatment of chronic angina. **Because Ranexa prolongs the QT interval, it should be reserved for patients who have not achieved an adequate response with other antianginal drugs.**

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and immediate container and carton labels submitted December 14, 2005. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-526.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and

effectiveness of the product in pediatric patients unless this requirement is waived or deferred. Please refer to our letter dated August 31, 2001 waiving the pediatric study requirement for this application.

We remind you of the following FDA dissolution specifications:

Condition	FDA Recommendation
Dissolution Medium	0.1N HCl
Paddle Speed	(b)(4) n
USP Apparatus II	
Volume	(b)(4) L
Specifications	0.5 h: (b)(4)
	4.0 h
	12.0 h
	20.0 h

We disagree with your proposal to drop the 12-hour assessment because we consider it important to showing the sustained-release properties of Ranexa.

Further, a retest date of (b)(4) for the drug substance and an expiration dating period of (b)(4) for the drug product will be granted based the stability data provided.

We remind you of the following postmarketing study commitment:

1. The impact of renal impairment on exposure to ranolazine should be better defined. One way of achieving this would be to re-do the population pharmacokinetics of ranolazine using the entire database available including patients with renal impairment. The report of the re-analysis should be submitted to the Agency by July 27, 2006.

   Protocol Submission: Not Applicable
   Study Start: Not Applicable
   Final Report Submission: by 07/06

2. Alternatively, a new pharmacokinetic study should be performed in patients with different degrees of renal impairment. The report of this study should be submitted to the Agency by January 2008.

   Protocol Submission: Not Applicable
   Study Start: Not Applicable
   Final Report Submission: by 01/08

Depending on the review of the population pharmacokinetics, you may be released from your commitment to perform the study in renal impairment.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual

report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence.**"

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Cardiovascular and Renal Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any question, please call:

Meg Pease-Fye, M.S.
Regulatory Project Manager
(301) 796-1130

Sincerely,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: agreed-upon labeling text

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

/s/

Robert Temple
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