

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-526/S004**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 21-526

SUPPL # 004

HFD # 110

Trade Name Ranexa

Generic Name ranolazine

Applicant Name CV Therapeutics

Approval Date, If Known

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒

NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

SE 1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒

NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, **EXPLAIN** why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

CVT 3036 or MERLIN-TIMI 36, a double-blind, placebo-controlled, international study conducted in patients within 48 hours of onset of acute coronary syndrome.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 43,735	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

Investigation #2		!
		!
IND #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐

Explain:

!

!

! NO ☐

! Explain:

Investigation #2

YES ☐

Explain:

!

!

! NO ☐

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐

NO ☐

If yes, explain:

=====

Name of person completing form: John David

Title: RPM

Date: 11/6/08

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.

Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05



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

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Norman Stockbridge  
11/6/2008 11:53:56 AM

**PEDIATRIC PAGE**

**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 21-526

Supplement Number: 004

NDA Supplement Type (e.g. SE5): SE1

Division Name: DCaRP

PDUFA Goal Date: 7/27/08

Stamp Date: 9/27/2007

Proprietary Name: Ranexa

Established/Generic Name: ranolazine

Dosage Form: 500 and 1000 mg Extended-Release (ER) Tablets

Applicant/Sponsor: CV Therapeutics

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

(1) 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. Ranexa should be used in combination with amlodipine, beta blockers or nitrates. The effect on angina rate or exercise tolerance appeared to be smaller in women than men

(2) \_\_\_\_\_

(3) \_\_\_\_\_

(4) \_\_\_\_\_

**Q1:** Is this application in response to a PREA PMC?

Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_

Supplement #: \_\_\_\_\_

PMC #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMC?

☐ Yes. **Skip to signature block.**

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s); ☒ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?\*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**\* Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): <sup>(b) (4)</sup>

(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** -S-004 The treatment of chronic angina. The second-line restriction on the use of ranolazine to treat patients with chronic stable angina is removed..(AP)

(b) (4)

**Q3:** Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

☒ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for the remaining pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

<b>Section A: Fully Waived Studies (for all pediatric age groups)</b>
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Reason(s) for full waiver: (**check, and attach a brief justification**)

☒ Necessary studies would be impossible or highly impracticable because:

☒ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): \_\_\_\_\_

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

				Reason (see below for further detail):			
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ** Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

☐ Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.**

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †	
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____								

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

**Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.**

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

(Revised: 4/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** \_\_\_\_\_

**Q1:** Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
- ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for the remaining pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

<b>Section A: Fully Waived Studies (for all pediatric age groups)</b>
---

Reason(s) for full waiver: **(check, and attach a brief justification)**

- ☐ Necessary studies would be impossible or highly impracticable because:
- ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): \_\_\_\_\_
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.*



**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ** Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

☐ Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.**

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †	
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____								

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

**Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.**

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

***If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.***

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 4/2008)

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.**

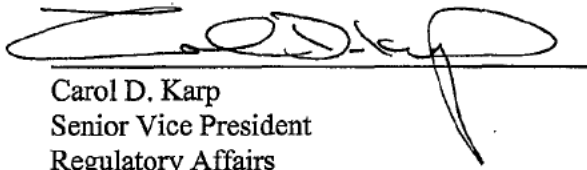
-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

-----  
John David  
11/6/2008 02:44:24 PM

1.3.3 Debarment Certification

CV Therapeutics, Inc., 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.



Carol D. Karp  
Senior Vice President  
Regulatory Affairs  
Quality and Drug Safety

August 3, 2007  
Date

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 21-526 BLA #	NDA Supplement # S-004 BLA STN #	If NDA, Efficacy Supplement Type: SE 1
Proprietary Name: Ranexa Established/Proper Name: ranolazine Dosage Form: 500 and 1000 mg Extended-Release (ER) Tablets		Applicant: CV Therapeutics Agent for Applicant (if applicable):
RPM: John David		Division: DCaRP
<b>NDAs:</b> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  (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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		<b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):  Provide a brief explanation of how this product is different from the listed drug.  <input type="checkbox"/> If no listed drug, check here and explain:  <b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b>  <input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:  <b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b>  <b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b>
❖ User Fee Goal Date Action Goal Date (if different)		7/27/08
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising MUST have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application <sup>2</sup> Characteristics		
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):  <div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> Fast Track  <input type="checkbox"/> Rolling Review  <input type="checkbox"/> Orphan drug designation         </div> <div> <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Direct-to-OTC         </div> </div> <div style="display: flex; justify-content: space-between;"> <div>           NDAs: Subpart H  <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)            Subpart I  <input type="checkbox"/> Approval based on animal studies    <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC         </div> <div>           BLAs: Subpart E  <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)            Subpart H  <input type="checkbox"/> Approval based on animal studies         </div> </div> Comments:		
❖ Application Integrity Policy (AIP) <a href="http://www.fda.gov/ora/compliance_ref/aip_page.html">http://www.fda.gov/ora/compliance_ref/aip_page.html</a>		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP <ul style="list-style-type: none"> <li>• If yes, exception for review granted (<i>file Center Director's memo in Administrative/Regulatory Documents section, with Administrative Reviews</i>)</li> <li>• If yes, OC clearance for approval (<i>file communication in Administrative/Regulatory Documents section with Administrative Reviews</i>)</li> </ul>		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Yes  <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Date reviewed by PeRC ( <i>required for approvals only</i> ) If PeRC review not necessary, explain: <input type="checkbox"/>		7/9/08
❖ BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM ( <i>approvals only</i> )		<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )		<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )		
• Office of Executive Programs (OEP) liaison has been notified of action		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Press Office notified of action		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated		<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new RMS-BLA Product Information Sheet for TBP must be completed.



❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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### CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist <sup>3</sup>	11/6/08
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/nonconsent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) Approved 11/5/08
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	11/4/08
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	11/3/04
❖ Original applicant-proposed labeling	9/27/07
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	previously approved label
❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	11/4/08

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.

❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	11/3/08
❖ Original applicant-proposed labeling	9/27/08
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	previously approved label
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date at upper right of first page of each submission</i> )	
❖ Most-recent division proposal for (only if generated after latest applicant submission)	N/A
❖ Most recent applicant-proposed labeling	N/A
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> RPM <input type="checkbox"/> DMEDP <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 3/10/08 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews SEALD 6/12/08, 11/3/08
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	11/6/08
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> <li>Center Director's Exception for Review memo</li> <li>If approval action, OC clearance for approval</li> </ul>	<input checked="" type="checkbox"/> Not on AIP
❖ Pediatric Page ( <i>approvals only, must be reviewed by PERC before finalized</i> )	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies <ul style="list-style-type: none"> <li>Outgoing communications (<i>if located elsewhere in package, state where located</i>)</li> <li>Incoming submissions/communications</li> </ul>	<input checked="" type="checkbox"/> None
❖ Postmarketing Commitment (PMC) Studies <ul style="list-style-type: none"> <li>Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>)</li> <li>Incoming submission documenting commitment</li> </ul>	<input checked="" type="checkbox"/> None
❖ Outgoing communications ( <i>letters (except previous action letters), emails, faxes, telecons</i> )	6/23/08, 12/3/07, 11/29/07, 10/25/07
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings <ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> <li>Regulatory Briefing (<i>indicate date</i>)</li> <li>Pre-NDA/BLA meeting (<i>indicate date</i>)</li> <li>EOP2 meeting (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> Not applicable <input checked="" type="checkbox"/> No mtg <input type="checkbox"/> No mtg 6/27/07 <input checked="" type="checkbox"/> No mtg

<sup>4</sup> Filing reviews for other disciplines should be filed behind the discipline tab.

• Other (e.g., EOP2a, CMC pilot programs)	SPA 7/24/04
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 11/3/08, 7/21/08
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 7/21/08
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	10/23/08, 7/21/08
• Clinical review(s) ( <i>indicate date for each review</i> )	10/20/08 (2), 9/26/08 (2), 9/24/08 (2), 9/22/08, 4/21/08
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )	N/A
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	6/6/08
❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ REMS • REMS Document and Supporting Statement ( <i>indicate date(s) of submission(s)</i> ) • Review(s) and recommendations (including those by OSE and CSS) ( <i>indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> None
❖ DSI Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
• Clinical Studies	
• Bioequivalence Studies	
• Clinical Pharmacology Studies	
<b>Clinical Microbiology</b>	<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
<b>Biostatistics</b>	<input type="checkbox"/> None
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/21/08
<b>Clinical Pharmacology</b>	<input type="checkbox"/> None

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 5/28/08
❖ DSI Clinical Pharmacology Inspection Review Summary	<input type="checkbox"/> None N/A
<b>Nonclinical</b> <input checked="" type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary	<input checked="" type="checkbox"/> None requested
<b>CMC/Quality</b> <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/TeamLeader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 6/25/08
• BLAs only: Facility information review(s) <i>(indicate dates)</i>	<input checked="" type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input checked="" type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	6/25/08
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
• BLAs: ➤ TBP-EER	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
➤ Compliance Status Check (approvals only, both original and all	Date completed:

<p>supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i></p>	<p><input type="checkbox"/> Requested  <input type="checkbox"/> Accepted    <input type="checkbox"/> Hold</p>
<p>❖ NDAs: Methods Validation</p>	<p><input type="checkbox"/> Completed  <input type="checkbox"/> Requested  <input type="checkbox"/> Not yet requested  <input checked="" type="checkbox"/> Not needed</p>

## Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

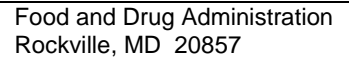
If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.



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/s/

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John David  
11/10/2008 10:47:39 AM



usubjid	
CVT3036_86076032	
CVT3036_94096001	

(b) (6)

If you have any questions, please call Mr. John David, Regulatory Project Manager at (301) 796-1059.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Norman Stockbridge  
6/23/2008 01:29:10 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>			
TO (Office/Division): <b>OPS Staff</b> <b>Attn: Raanan Bloom (301-796-2185)</b> <b>WO21 RM 3515</b>			FROM (Name, Office/Division, and Phone Number of Requestor): <b>Teshara G. Bouie, ONDQA, Division of Post-Marketing Assessment, 301-796-1649</b>		
DATE <b>MArch 13, 2008</b>	IND NO.	NDA NO. <b>NDA 21-526</b>	TYPE OF DOCUMENT <b>SE1-004</b>	DATE OF DOCUMENT <b>September 27, 2007</b>	
NAME OF DRUG <b>Ranexa</b>		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE <b>June 1, 2008</b>	
NAME OF FIRM: <b>CV Therap</b>					
<b>REASON FOR REQUEST</b>					
<b>I. GENERAL</b>					
<div> <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER </div> <div> <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END-OF-PHASE 2a MEETING <input type="checkbox"/> FINAL PRINTED LABELING </div> <div> <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> LABELING REVISION </div> <div> <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE </div> <div> <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> SAFETY / EFFICACY <input type="checkbox"/> FORMULATIVE REVIEW </div> <div> <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION <input type="checkbox"/> PAPER NDA <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): </div> <div> <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> CONTROL SUPPLEMENT </div>					
<b>II. BIOMETRICS</b>					
<input type="checkbox"/> PRIORITY P NDA REVIEW <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILTY STUDIES <input type="checkbox"/> PHASE 4 STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG SAFETY</b>					
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> NONCLINICAL		
<b>COMMENTS / SPECIAL INSTRUCTIONS:</b> This supplement provides for the use of Ranexa as first-line therapy for the long-term treatment of chronic angina. Please review. This supplement is located in the EDR.					
SIGNATURE OF REQUESTOR <b>Teshara G. Bouie</b>			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER		

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/s/

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Teshara Bouie  
3/13/2008 09:46:15 AM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-526 S-004/ (b) (4)

CV Therapeutics, Inc.  
Attention: Carol D. Karp  
3172 Porter Drive  
Palo Alto, CA 94304

Dear Ms. Karp:

Please refer to your supplemental new drug application(s) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ranexa (ranolazine) 500 and 1000 mg Extended-Release (ER) Tablets.

We also refer to your submission dated December 19, 2007, received December 20, 2007, containing a request for a waiver of the 4-month safety update.

We have considered your request and have granted a waiver for S-004/ (b) (4)

If you have any questions, please call Mr. John David, Regulatory Health Project Manager, at (301) 796-1059.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Norman Stockbridge  
1/24/2008 04:17:21 PM





DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-526/S-004

CV Therapeutics  
Attention: Carol D. Karp  
3172 Porter Drive  
Palo Alto, CA 94304

Dear Ms. Karp:

Please refer to your supplemental new drug application (NDA) dated September 27, 2007, received September 27, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Ranexa (ranolazine) 500 and 1000 mg Extended-Release (ER) Tablets.

We also refer to your submissions dated October 18, 23 and November 26, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is July 27, 2008.

In your cover letter for this submission, you cite 4 reasons for considering this application for Priority review. The first was that the results presented reduce a treatment-limiting safety concern. This echoes and references MaPP 6020.3, but wholly out of context. The reference in 6020.3 appears as an illustration of how a new therapy might represent a significant advance over existing therapeutic alternatives, not that this specific product might be less unsafe than previously feared. (b) (4)

We also request that you submit the following information:

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?

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please call Mr. John David, Regulatory Project Manager at (301) 796-1059.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Norman Stockbridge  
12/3/2007 04:56:15 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<h2 style="margin: 0;">REQUEST FOR CONSULTATION</h2>		
TO (Division/Office): <b>Office of Surveillance and Epidemiology (OSE)</b> <b>Attention: Darrell Jenkins, RPM</b>			FROM: CDR John David	
DATE 12/3/07	IND NO.	NDA NO. 21-526. S-004 (b) (4)	TYPE OF DOCUMENT NDA Supplement (b) (4)	DATE OF DOCUMENT 9/27/07
NAME OF DRUG Ranexa (ranolazine)		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 3/3/08
NAME OF FIRM: CV Therapeutics				
REASON FOR REQUEST				
I. GENERAL				
<div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> <input type="checkbox"/> NEW PROTOCOL  <input type="checkbox"/> PROGRESS REPORT  <input type="checkbox"/> NEW CORRESPONDENCE  <input type="checkbox"/> DRUG ADVERTISING  <input type="checkbox"/> ADVERSE REACTION REPORT  <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION  <input type="checkbox"/> MEETING PLANNED BY         </div> <div style="width: 30%;"> <input type="checkbox"/> PRE-NDA MEETING  <input type="checkbox"/> END OF PHASE II MEETING  <input type="checkbox"/> RESUBMISSION  <input type="checkbox"/> SAFETY/EFFICACY  <input type="checkbox"/> PAPER NDA  <input type="checkbox"/> CONTROL SUPPLEMENT         </div> <div style="width: 30%;"> <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER  <input type="checkbox"/> FINAL PRINTED LABELING  <input type="checkbox"/> LABELING REVISION  <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE  <input type="checkbox"/> FORMULATIVE REVIEW  <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):         </div> </div>				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: Please review the tradename & labeling for NDA 21-526 Ranexa (ranolazine) 500 and 1000 mg Extended-Release (ER) Tablets and provide comments. This (b) (4) was submitted on 9/27/07. <b>1) S-004:</b> first-line therapy for the long-term treatment of chronic angina. (b) (4) <div style="background-color: #cccccc; height: 20px; width: 100%; margin-top: 5px;"></div> <div style="background-color: #cccccc; height: 20px; width: 100%; margin-top: 5px;"></div> <div style="background-color: #cccccc; height: 20px; width: 100%; margin-top: 5px;"></div> <div style="background-color: #cccccc; height: 20px; width: 100%; margin-top: 5px;"></div>				
<div style="background-color: #cccccc; height: 20px; width: 100%; margin-bottom: 5px;"></div> This submission is located in the EDR. Thank you!				
SIGNATURE OF REQUESTER CDR John David			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> EMAIL <span style="float: right;"><input type="checkbox"/> HAND</span>	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

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/s/

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John David  
12/3/2007 08:21:29 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			<h2 style="margin: 0;">REQUEST FOR CONSULTATION</h2>	
TO (Division/Office): Lisa Hubbard, RPh, Regulatory Review Officer, Division of DrugMarketing, Advertising, and Communication (DDMAC)			FROM: CDR John David	
DATE 12/3/07	IND NO.	NDA NO. 21-526. S-004 (b) (4)	TYPE OF DOCUMENT DDMAC Consult	DATE OF DOCUMENT 9/27/07
NAME OF DRUG Ranexa (ranolazine)		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 3/3/08
NAME OF FIRM: United Therapeutics				
<b>REASON FOR REQUEST</b>  <b>I. GENERAL</b>				
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <input type="checkbox"/> NEW PROTOCOL  <input type="checkbox"/> PROGRESS REPORT  <input type="checkbox"/> NEW CORRESPONDENCE  <input type="checkbox"/> DRUG ADVERTISING  <input type="checkbox"/> ADVERSE REACTION REPORT  <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION  <input type="checkbox"/> MEETING PLANNED BY         </div> <div style="width: 33%;"> <input type="checkbox"/> PRE--NDA MEETING  <input type="checkbox"/> END OF PHASE II MEETING  <input type="checkbox"/> RESUBMISSION  <input type="checkbox"/> SAFETY/EFFICACY  <input type="checkbox"/> PAPER NDA  <input type="checkbox"/> CONTROL SUPPLEMENT         </div> <div style="width: 33%;"> <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER  <input type="checkbox"/> FINAL PRINTED LABELING  <input type="checkbox"/> LABELING REVISION  <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE  <input type="checkbox"/> FORMULATIVE REVIEW  <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):         </div> </div>				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input checked="" type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: Please review the labeling for NDA 21-526 Ranexa (ranolazine) 500 and 1000 mg Extended-Release (ER) Tablets and provide comments. This (b) (4) was submitted on 9/27/07. <b>1) S-004:</b> first-line therapy for the long-term treatment of chronic angina. (b) (4)  <div style="background-color: #cccccc; height: 20px; width: 100%;"></div> <div style="background-color: #cccccc; height: 20px; width: 100%;"></div> <div style="background-color: #cccccc; height: 20px; width: 100%;"></div> <p style="margin-top: 10px;">This submission is located in the EDR. Thank you!</p>				
SIGNATURE OF REQUESTER CDR John David			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

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/s/

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John David  
12/3/2007 08:10:49 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-526/S-004

**PRIOR APPROVAL SUPPLEMENT**

CV Therapeutics, Inc.  
Attention: Carol D. Karp  
Senior Vice President  
Regulatory Affairs  
Quality and Drug Safety  
3172 Porter Drive  
Palo Alto, CA 94304

Dear Ms. Karp:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Ranexa® (ranolazine) Extended-release Tablets
NDA Number:	21-526
Supplement number:	S-004
Date of supplement:	September 27, 2007
Date of receipt:	September 27, 2007

This supplemental application proposes to expand the indication of Ranexa to first-line therapy for the long-term treatment of chronic angina.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 26, 2007 in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:



Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Cardiovascular and Renal Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, please contact:

Mr. John David  
Regulatory Project Manager  
(301)796-1059

Sincerely,

*{See appended electronic signature page}*

Edward Fromm  
Chief, Project Management Staff  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Edward Fromm

10/25/2007 02:13:22 PM