CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-526

Chemistry Review(s)

NDA 21-526

Ranexa™
(Ranolazine Extended Release Tablets)

CV Therapeutics

Kris Raman, Ph.D.
Division of Cardio-Renal Drug Products (HFD-110)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-526

2. REVIEW #: 4

3. REVIEW DATE: 1/11/06

4. REVIEWER: Kris Raman

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	December 30, 2002
Amendment	March 18, 2002
Amendment	April 4, 2003
Amendment	September 13, 2003
Amendment	October 9, 2003
Amendment	July 26, 2005
Amendment	October 27, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	December 14, 2005

7. NAME & ADDRESS OF APPLICANT:

Name: CV Therapeutics, Inc

Address: 3172 Porter Drive, Palo Alto, CA 94304

Representative: Carol D. Karp

Telephone: 650-384-8875

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ranexa
b) Non-Proprietary Name (USAN): Ranolazine

c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Treatment of Chronic Angina

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ✓ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

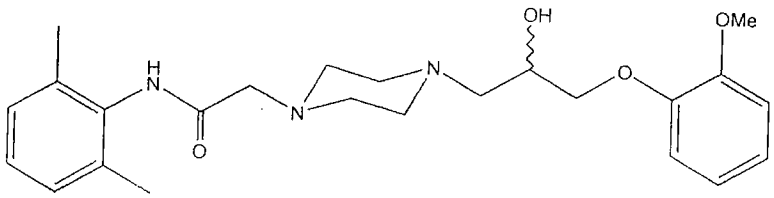
___✓___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-Piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)-;

(±)-4-[2-hydroxy-3-(o-methoxyphenoxy)propyl]-1-piperazineaceto-2',6'-xylidide

Molecular Formula $C_{24}H_{33}N_3O_4$ Molecular wt: 427.54



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM RFFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	IV			4	Adequate	9/8/03	
	III			3	Adequate	4/22/02	
	III			3	Adequate	2/3/02	
	III			4	Adequate	9/8/03	
	III			4	Adequate	9/8/03	
	III			3 & 4	Adequate	9/8/03	
	III			3	Adequate	3/22/01	
	III			3	Adequate	3/22/01	
	III			4	Adequate	9/8/03	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	30,205	Submitted on 6/10/1987
IND	43,735	Submitted on 10/19/1993

18. STATUS:

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Overall Acceptable	8/16/2005	S. Ferguson (HFD-322) J. D Ambrogio (HFD-322)
Pharm/Tox	N/A	--	--
Biopharm	Deletion of the 12 hour value ([redacted] dissolved) from the recommended dissolution specification is not acceptable. Therefore, the dissolution specifications recommended earlier by the Agency should be included.	11/30/05	Peter Hinderling, Ph.D.
LNC	N/A	--	--
Methods Validation	Pending	11/30/05	K. Raman
DMETS	Proprietary name "Ranexa" is acceptable. In the Amendment, dated 12/14/05, the applicant has agreed to implement the changes recommend by DMETS.	11/23/2005	D.P. Toyer
EA	The sponsor has stated that no additional information is available for this section. In addition, the sponsor has referenced the original NDA submission dated December 27, 2002, and all subsequent amendments.	7/26/05	K. Raman Also refer to Review I
Microbiology	N/A	--	--

The Chemistry Review for NDA 21-526

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for Approval from the stand point of chemistry, manufacturing, and controls. An overall acceptable recommendation was received from the Office of Compliance regarding manufacturing facilities on August 16, 2005. The applicant provided updated stability data [ ] on drug substance and the drug product, which is satisfactory. This review # 4 is in reference to CV Therapeutics response to DMETS comments, dated 11/23/05, on proposed labeling for ranolazine. The applicant has submitted the revised container labels and labeling for Ranexa, in accordance with DMETS recommendations.

The following statement regarding retest date for the drug substance, expiration date and dissolution specification for the drug product should be included in the action letter:

- A retest date of [ ] for the drug substance and an expiration dating period of [ ] for the drug product will be granted based the stability data provided.

- The recommended dissolution specifications for ranolazine 500 mg tablets is: USP Apparatus 2, paddle speed [ ] rpm , 0.1N HCl, [ ] vessel temperature 37°C ± 0.5°C, sampling time and acceptance criteria of 0.5 hr [ ] 4 hr , [ ] 12 hr , [ ] and 20 hr (NLT [ ]

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Ranolazine is a white to off-white solid [ ]. Ranolazine is synthesized [ ] The drug substance is a free base and freely soluble in buffered solutions at pH below 4.82. The solubility is found to be enhanced at lower pH , [ ] of Ranolazine. Ranolazine has one chiral center but is synthesized as a racemic compound. Ranolazine [ ]

] It does not [ ]

]

process. Specified and potential impurities in the drug substance have been characterized. Ranolazine has a number of specified impurities and they have been characterized. A [ ] retest date for the drug substance has been proposed in the submission. An updated stability data [ ] supports the proposed retest period.

Ranolazine drug product is formulated as an extended release tablet formulation in 500 mg strength (light orange colored) tablets. The extended release characteristics of the drug product is : [ ] Addition [ ] during manufacturing results in a [ ] particles and that are released over an extended period. The drug product contains a few other compendial excipients and is manufactured by [ ]. The tablets are not scored. The drug product is found to be stable up to 36 months at 25C/60%RH conditions and no degradation products were observed under all tested conditions. The proposed test methods are found to be adequate. The acceptance criteria are adequate to ensure identity, purity, quality, and potency of the drug product. The drug product will be stored in HDPE bottles. All packaging components are made of standard packaging components and based on stability, deemed adequate to protect the drug product through its shelf life. Based on updated stability data a thirty six (36) months expiry is granted for the drug product.

The proposed elimination of dissolution testing at 12 hour time point by the sponsor is not acceptable to the OCPB. According to OCPB (review, dated 11/30/05), deletion of the 12 hour value ([ ] dissolved) in the dissolution specifications proposed by the sponsor would result in accepting formulation with [ ] dissolution at 5 hours. In addition, drug delivery by such a formulation would profoundly alter the plasma concentration profile of ranolazine. Therefore, OCPB recommends that the dissolution specifications recommended earlier by the Agency should be maintained.

An expiration dating period of thirty six (36) months for 500 mg ranolazine tablets will be granted based the stability data provided.

The proprietary name "Ranexa" was found to be acceptable to the Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety.

In the original submission, dated December 30, 2002, [ ] and 500 mg, of ranolazine tablets were proposed. However, in the current amendment the [ ] is not included in the proposed labeling for Ranexa Package Insert. Therefore, the [ ] has not been evaluated in this review.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended to be used orally with 500 mg as initial dose but higher dose of 1000 mg b.i.d., could be administered based on clinical response. Ranexa should be swallowed as whole tablet. Ranexa may be taken with or without meals. Ranexa seems to be well tolerated when administered with other commonly administered cardiovascular medications (beta-blockers, antihypertensive agents, calcium agonists and nitrates).

C. Basis for Approvability or Not-Approval Recommendation

There are no pending CMC issues in the submission. The drug substance and drug product stability data has been updated [ ] and some changes have been made to the drug product dissolution specifications. This application is recommended for Approval from the stand point of chemistry, manufacturing, and controls.

An overall acceptable recommendation was received from the Office of Compliance regarding manufacturing facilitates on August 16, 2005. The following statement regarding retest date for the drug substance, expiration date and dissolution specification for the drug product should be included in the action letter:

- A retest date of [ ] for the drug substance and an expiration dating period of thirty six (36) months for the drug product will be granted based the stability data provided.

- The recommended dissolution specifications for ranolazine 500 mg tablets is: USP Apparatus 2, paddle speed [ ], 0.1N HCl, [ ], vessel temperature 37°C ± 0.5°C, sampling time and acceptance criteria of 0.5 hr [ ] 4 hr [ ] 12 hr [ ] and 20 hr (NLT [ ]).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist: Kris Raman, Ph.D./Date: 1/11/06
Chemistry Team Leader: Kasturi Srinivasachar, Ph.D./Date:1/11/06
Project Manager: Meg Pease-Fye/Date: 1/11/06

C. CC Block

Original NDA 21-526
HFD-110/Division File
HFD-110/Team Leader/Kasturi Srinivasachar, Ph.D.
HFD-810/Chemistry Division Director/John Simmons, Ph.D.

6 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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

/s/

Kris Raman
1/11/2006 12:00:54 PM
CHEMIST

Kasturi Srinivasachar
1/11/2006 06:28:28 PM
CHEMIST

NDA 21-526

Ranexa™
(Ranolazine Extended Release Tablets)

CV Therapeùtics

Kris Raman, Ph.D.
Division of Cardio-Renal Drug Products (HFD-110)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-526

2. REVIEW #: 3

3. REVIEW DATE: 12/16/05

4. REVIEWER: Kris Raman

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	December 30, 2002
Amendment	March 18, 2002
Amendment	April 4, 2003
Amendment	September 13, 2003
Amendment	October 9, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	July 26, 2005
Amendment	October 27, 2005

7. NAME & ADDRESS OF APPLICANT:

Name: CV Therapeutics, Inc

Address: 3172 Porter Drive, Palo Alto, CA 94304

Representative: Carol D. Karp

Telephone: 650-384-8875

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ranexa
b) Non-Proprietary Name (USAN): Ranolazine
c) Code Name/# (ONDC only):

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Treatment of Chronic Angina

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ✓ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

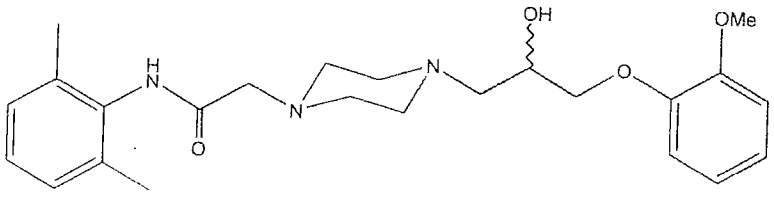
✓ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-Piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)-;

(±)-4-[2-hydroxy-3-(o-methoxyphenoxy)propyl]-1-piperazineaceto-2',6'-xylidide

Molecular Formula $C_{24}H_{33}N_3O_4$ Molecular wt: 427.54



17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	IV	[redacted]	[redacted]	4	Adequate	9/8/03	
	III			3	Adequate	4/22/02	
	III			3	Adequate	2/3/02	
	III			4	Adequate	9/8/03	
	III			4	Adequate	9/8/03	
	III			3 & 4	Adequate	9/8/03	
	III			3	Adequate	3/22/01	
	III			3	Adequate	3/22/01	
[redacted]	III	[redacted]	[redacted]	4	Adequate	9/8/03	

[1] Action codes for DMF Table:
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2 –Type 1 DMF
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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	30,205	Submitted on 6/10/1987
IND	43,735	Submitted on 10/19/1993

18. STATUS:

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Overall Acceptable	8/16/2005	S. Ferguson (HFD-322) J. D Ambrogio (HFD-322)
Pharm/Tox	N/A	--	--
Biopharm	Deletion of the 12 hour value [ ] dissolved) from the recommended dissolution specification is not acceptable. Therefore, the dissolution specifications recommended earlier by the Agency should be included.	11/30/05	Peter Hinderling, Ph.D.
LNC	N/A	--	--
Methods Validation	Pending	11/30/05	K. Raman
DMETS	Proprietary name "Ranexa" is acceptable	11/23/2005	D.P. Toyer
EA	The sponsor has stated that no additional information is available for this section. In addition, the sponsor has referenced the original NDA submission dated December 27, 2002, and all subsequent amendments.	7/26/05	K. Raman Also refer to Review I
Microbiology	N/A	--	--

The Chemistry Review for NDA 21-526

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for Approval from the stand point of chemistry, manufacturing, and controls. An overall acceptable recommendation was received from the Office of Compliance regarding manufacturing facilitates on August 16, 2005. The applicant provided updated stability data [ ] on drug substance and the drug product, which appears satisfactory. The following statement regarding retest date for the drug substance, expiration date and dissolution specification for the drug product should be included in the action letter:

- A retest date of [ ] for the drug substance and an expiration dating period of thirty six (36) months for the drug product will be granted based the stability data provided.

- The recommended dissolution specifications for ranolazine 500 mg tablets is: USP Apparatus 2, paddle speed [ ] 0.1N HCl [ ] vessel temperature 37°C ± 0.5°C, sampling time and acceptance criteria of 0.5 hr [ ] 4 hr [ ] 12 hr [ ] and 20 hr (NLT [ ]

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Ranolazine is a white to off-white solid [ ] Ranolazine is synthesized in [ ] The drug substance is a free base and freely soluble in buffered solutions at pH below 4.82. The solubility is found to be enhanced at lower pH [ ] of Ranolazine. Ranolazine has one chiral center but is synthesized as a racemic compound.] [

] . It does not [

process. Specified and potential impurities in the drug substance have been characterized. Ranolazine has a number of specified impurities and they have been characterized. A [ ] retest date for the drug substance has been proposed in the submission. An updated stability data [ ] supports the proposed retest period.

Ranolazine drug product is formulated as an extended release tablet formulation in 500 mg strength (light orange colored) tablets. The extended release characteristics of the drug product is achieved [ ]. Addition of [ ] during manufacturing results in a [ ] over an extended period. The drug product contains a few other compendial excipients and is manufactured by [ ]. The tablets are not scored. The drug product is found to be stable up to 36 months at 25C/60%RH conditions and no degradation products were observed under all tested conditions. The proposed test methods are found to be adequate. The acceptance criteria are adequate to ensure identity, purity, quality, and potency of the drug product. The drug product will be stored in HDPE bottles. All packaging components are made of standard packaging components and based on stability, deemed adequate to protect the drug product through its shelf life. Based on updated stability data a thirty six (36) months expiry is granted for the drug product.

The proposed elimination of dissolution testing at 12 hour time point by the sponsor is not acceptable to the OCPB. According to OCPB (review, dated 11/30/05), deletion of the 12 hour value ([ ] dissolved) in the dissolution specifications proposed by the sponsor would result in accepting formulation with [ ] dissolution at 5 hours. In addition, drug delivery by such a formulation would profoundly alter the plasma concentration profile of ranolazine. Therefore, OCPB recommends that the dissolution specifications recommended earlier by the Agency should be maintained.

An expiration dating period of thirty six (36) months for 500 mg ranolazine tablets will be granted based the stability data provided.

The proprietary name "Ranexa" was found to be acceptable to the Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety.

In the original submission, dated December 30, 2002, both strengths, 375 mg and 500 mg, of ranolazine tablets were proposed. However, in the current amendment the 375 mg tablet strength is not included in the proposed labeling for Ranexa Package Insert. Therefore, the 375 mg strength has not been evaluated in this review.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended to be used orally with 500 mg as initial dose but higher dose of 1000 mg b.i.d., could be administered based on clinical response. Ranexa should be swallowed as whole tablet. Ranexa may be taken with or without meals. Ranexa seems to be well tolerated when administered with other commonly administered cardiovascular medications (beta-blockers, antihypertensive agents, calcium agonists and nitrates).

C. Basis for Approvability or Not-Approval Recommendation

There are no pending CMC issues in the submission. The drug substance and drug product stability data has been updated [ ] and some changes have been made to the drug

product dissolution specifications. This application is recommended for Approval from the stand point of chemistry, manufacturing, and controls.

An overall acceptable recommendation was received from the Office of Compliance regarding manufacturing facilitates on August 16, 2005. The following statement regarding retest date for the drug substance, expiration date and dissolution specification for the drug product should be included in the action letter:

- A retest date [ ] for the drug substance and an expiration dating period of thirty six (36) months for the drug product will be granted based the stability data provided.

- The recommended dissolution specifications for ranolazine 500 mg tablets is: USP Apparatus 2, paddle speed [ ], 0.1N HCl, [ ] vessel temperature 37°C ± 0.5°C, sampling time and acceptance criteria of 0.5 hr [ ], 4 hr [ ], 12 hr [ ] and 20 hr (NLT [ ].

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist: Kris Raman, Ph.D./Date: 12/16/05
Chemistry Team Leader: Kasturi Srinivasachar, Ph.D./Date: 12/16/05
Project Manager: Meg Pease-Fye/Date

C. CC Block

Original NDA 21-526
HFD-110/Division File
HFD-110/Team Leader/Kasturi Srinivasachar, Ph.D.
HFD-810/Chemistry Division Director/John Simmons, Ph.D.

12 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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

/s/

Kris Raman
12/16/2005 01:03:59 PM
CHEMIST

Kasturi Srinivasachar
12/16/2005 01:11:54 PM
CHEMIST

NDA 21-526

Ranexa

Ranolazine Extended Release Tablets
375 mg and 500 mg

CV Therapeutics, Inc.

N. Chidambaram Ph.D.
Cardio-Renal Drug Products (HFD-110)

Table of Contents

Appears This Way
On Original

Chemistry Review Data Sheet

1. NDA 21-526

2. REVIEW #: 2

3. REVIEW DATE: 10.10.03

4. REVIEWER: Nallaperumal Chidambaram

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	December 30, 2002
Amendment	March 18, 2003
Amendment	April 4, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	September 13, 2003
Amendment (Fax)	October 9, 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	CV Therapeutics, Inc.
Address:	3172 Porter drive, Palo Alto, CA 94304
Representative:	Carol D. Karp, VP, Regulatory Affairs
Telephone:	(650) 384-8875

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ranexa
b) Non-Proprietary Name (USAN): Ranolazine (Applied for)
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Treatment of Chronic Angina

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 375 and 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ✓ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

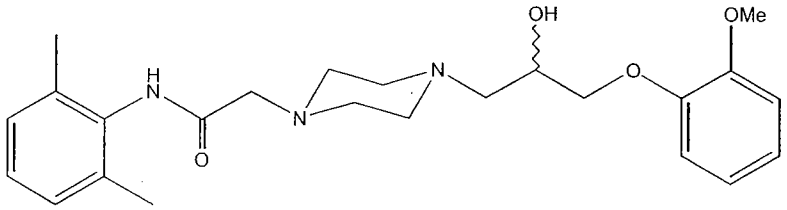
___✓___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-Piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)-;

(±)-4-[2-hydroxy-3-(o-methoxyphenoxy)propyl]-1-piperazineaceto-2',6'-xylidide

$C_{24}H_{33}N_3O_4$ 427.54



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[	IV	[	[	4	Adequate	09.08.2003	
	III			3	Adequate	04.22.2002	
	III			3	Adequate	02.03.2002	
	III			4	Adequate	09.08.2003	
	III			4	Adequate	09.08.2003	
	III			3 & 4	Adequate	09.08.2003	
	III			3	Adequate	03.22.2001	
	III			3	Adequate	03.22.2001	
]	III	]	]	4	Adequate	09.08.2003	

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4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	30,205	Submitted on 06.10.1987
IND	43,735	Submitted on 10.19.1993

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Overall Acceptable	10.06.2003	J.D. Ambrogio
Pharm/Tox	N/A		
Biopharm	Dissolution specification changes recommended	09.15.2003	Peter Hinderling
LNC	N/A		
Methods Validation	Pending	10.07.2003	N. Chidambaram
OPDRA	Proprietary Name "Ranexa" acceptable	05.23.2003	D.P. Toyer
EA	Categorical Exclusion	09.08.2003	N. Chidambaram
Microbiology	N/A		

The Chemistry Review for NDA 21-526

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for APPROVAL from the stand point of chemistry, manufacturing and controls since satisfactory responses were received to all of the deficiencies concerning drug substance and drug product that were identified and conveyed to the applicant. An overall acceptable recommendation was received from the Office of Compliance regarding manufacturing facilities on October 6, 2003 (see attached). The following statement regarding retest date for the drug substance and expiration date for the drug product should be included in the action letter:

- A retest date [ ] for the drug substance and an expiration-dating period of [ ] the drug product will be granted based on the stability data provided.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Ranolazine is a white to off-white solid [ ]. Ranolazine is synthesized [ ] The drug substance is a free base and is freely soluble in buffered solutions at pH below 4.82. The solubility is found to be enhanced at lower pH [ ] of ranolazine. The solubility of ranolazine is highest in dichloromethane amongst organic solvents and is progressively lower going from dichloromoethane to methanol, tetrahydrofuran and ethanol. It is very slightly soluble in isopropanol, toluene and ethyl ether. Ranolazine has one chiral center but is synthesized as a racemic compound. [

] It does not [ ]

process. Specified and potential impurities in the drug substance have been characterized. Ranolazine has a number of specified impurities and they have

been characterized. Validated analytical methods were provided in the submission. [ ] retest was proposed and provided test data and a reasonable extrapolation of primary stability data supports a retest period of [ ]

Ranolazine drug product is formulated as an extended release tablet formulation in [ ] 500 mg (Light orange) colored tablets. The extended release characteristics of the drug product is achieved [ ] Addition of [ ] over an extended period. The drug product contains a few other compendial excipients and is manufactured by [ ] The tablets are not scored. The drug product is found to be stable [ ] at 25°C/60%RH conditions and no degradation products were observed under all tested conditions. The proposed test methods are found to be adequate. The acceptance criteria are adequate to ensure identity, purity, quality and potency of the drug product. The drug product will be stored in HDPE bottles. All packaging components are made of standard packaging components and based on stability, deemed adequate to protect the drug product through its shelf life. The applicant has proposed [ ] shelf life. However, based on provided primary and supportive stability data and also based on a reasonable extrapolation of primary stability data, [ ] of expiry is granted. Validated analytical methods were provided in the submission.

The trade name Ranexa was found to be acceptable to the Division of medication Errors and Technical Support (DMETS), Office of Drug Safety.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended to be used orally with 500 mg as a starting dose twice daily [ ] 1000 mg b.i.d., could be considered based on clinical response. Ranexa should be swallowed as a whole tablet and should not be crushed, broken or chewed. Ranexa may be taken with or without meals. Ranexa seems to be well tolerated when administered with other commonly administered cardiovascular medications (beta-blockers, anti-hypertensive agents, calcium agonists and nitrates).

C. Basis for Approvability or Not-Approval Recommendation

This application is recommended for APPROVAL since all of the deficiencies that were identified and conveyed to the applicant have been satisfactorily addressed. Data from a routine test [ ] of the drug substance were provided. The acceptance criteria were tightened as recommended, and a stability commitment was also provided.

The drug product release specification was tightened as recommended. A mechanism for drug release was provided. The applicant has agreed to other recommended changes with respect to labeling. The applicant also indicated that they have applied for an USAN name.

An overall satisfactory recommendation was received from the Office of Compliance on October 6, 2003 (see attached). The following statement regarding retest date for the drug substance and expiration date for the drug product should be included in the action letter:

- A retest date of [ ] for the drug substance and an expiration-dating period of [ ] for the drug product will be granted based on the stability data provided.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist: Nallaperumal Chidambaram / Date: October 10, 2003
Chemistry Team Leader: Kasturi Srinivasachar / Date:
ProjectManager Meg Pease-Fye / Date

C. CC Block

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Nallaperumal Chidambaram
10/10/03 02:25:20 PM
CHEMIST

Kasturi Srinivasachar
10/10/03 02:46:42 PM
CHEMIST

NDA 21-526

Ranexa

Ranolazine Extended Release Tablets
375 mg and 500 mg

CV Therapeutics, Inc.

N. Chidambaram Ph.D.
Cardio-Renal Drug Products (HFD-110)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-526

2. REVIEW #: 1

3. REVIEW DATE: 09.16.03

4. REVIEWER: Nallaperumal Chidambaram

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	December 30, 2002
Amendment	March 18, 2003
Amendment	April 4, 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	CV Therapeutics, Inc.
Address:	3172 Porter drive, Palo Alto, CA 94304
Representative:	Carol D. Karp, VP, Regulatory Affairs
Telephone:	(650) 384-8875

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ranexa
b) Non-Proprietary Name (USAN): Ranolazine
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Treatment of Chronic Angina

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 375 and 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ✓ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

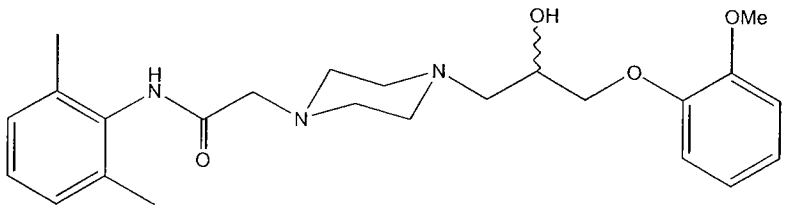
✓ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-Piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)-;

(±)-4-[2-hydroxy-3-(o-methoxyphenoxy)propyl]-1-piperazineaceto-2',6'-xylidide

$C_{24}H_{33}N_3O_4$ 427.54



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	IV	[redacted]	[redacted]	4	Adequate	09.08.2003	
	III			3	Adequate	04.22.2002	
	III			3	Adequate	02.03.2002	
	III			4	Adequate	09.08.2003	
	III			4	Adequate	09.08.2003	
	III			3 & 4	Adequate	09.08.2003	
	III			3	Adequate	03.22.2001	
	III			3	Adequate	03.22.2001	
[redacted]	III	[redacted]	[redacted]	4	Adequate	09.08.2003	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	30,205	Submitted on 06.10.1987
IND	43,735	Submitted on 10.19.1993

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	09.08.2003	
Pharm/Tox	N/A		
Biopharm	Dissolution specification changes recommended	09.15.2003	Peter Hinderling
LNC	N/A		
Methods Validation	Pending	09.08.2003	N. Chidambaram
OPDRA	Proprietary Name "Ranexa" acceptable	05.23.2003	D.P. Toyer
EA	Categorical Exclusion	09.08.2003	N. Chidambaram
Microbiology	N/A		

The Chemistry Review for NDA 21-526

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is APPROVABLE from the stand point of chemistry, manufacturing and controls provided satisfactory responses are received to the deficiencies concerning drug substance and drug product that were identified and conveyed to the applicant and in addition an overall satisfactory recommendation is received from the Office of Compliance regarding manufacturing facilities. Inspection of the drug substance manufacturing facility has been scheduled but not yet completed.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Ranolazine is a white to off-white solid [ ] Ranolazine is synthesized [ ] The drug substance is a free base and is freely soluble in buffered solutions at pH below 4.82. The solubility is found to be enhanced at lower pH [ ] ranolazine. The solubility of ranolazine is highest in dichloromethane amongst organic solvents and is progressively lower going from dichloromoethane, methanol, tetrahydrofuran and ethanol. It is very slightly soluble in isopropanol, toluene and ethyl ether. Ranolazine has one chiral center but is synthesized as a racemic compound. [

] It does not [

] Specified and potential impurities in the drug substance have been characterized. Ranolazine has a number of specified impurities and they have been characterized. Validated analytical methods were provided in the submission. [ ] retest was proposed and provided test data and a reasonable extrapolation of primary stability data supports a retest period of [ ]. An extension of retest period could be considered once additional data becomes available.

Ranolazine drug product is formulated as an extended release tablet formulation in [ ] 500 mg (Light orange) colored tablets. Methacryllic acid copolymer is an compendial excipient [ ] of the drug product. The drug product is released over 24 h time point. The drug product contains a few other compendial excipients. The drug product is manufactured by [ ]. The tablets are not scored. The drug product is found to be stable [ ] at 25°C/60%RH conditions and no degradation products were observed under all tested conditions. The proposed test methods are found to be adequate. The acceptance criteria are adequate to ensure identity, assay, degradation products and uniformity of dosage units. The ranolzaine drug product will be stored in HDPE bottles. All packaging components are made of standard packaging components and based on stability, deemed adequate to protect the drug product through its shelf life. The applicant has proposed a [ ] shelf life based on primary and supportive stability data. However, based on provided primary and supportive stability data and also based on a reasonable extrapolation of primary stability data, [ ] of expiry is granted. Validated analytical methods were provided in the submission.

The trade name Ranexa was found to be acceptable to the Division of medication Errors and Technical Support (DMETS), Office of Drug Safety.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended to be used orally with 500 mg as a starting dose twice daily. [ ] 1000 mg b.i.d. Ranexa should be swallowed as a whole tablet and should not be crushed, broken or chewed. Ranexa may be taken with or without meals. Ranexa seems to be well tolerated when administered with other commonly administered cardiovascular medications (beta-blockers, anti-hypertensive agents, calcium agonists and nitrates).

C. Basis for Approvability or Not-Approval Recommendation

This application is APPROVABLE provided the deficiencies that were identified and conveyed to the applicant are satisfactorily addressed. The deficiencies include critical data from routine tests [ ] of the drug substance, tightening of acceptance criteria and stability commitment.

The deficiencies in the drug product section include release specification, mechanism of drug release, USAN name, addition of extended release tablets to established name and storage conditions.

Final recommendation could be given once satisfactory responses are received for the deficiencies and an overall satisfactory recommendation is received from the Office of Compliance (Please see page 80-81 for list of draft deficiencies).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist: Nallaperumal Chidambaram / Date: September 16, 2003
Chemistry Team Leader: Kasturi Srinivasachar / Date:
ProjectManager Meg Pease-Fye / Date

C. CC Block

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/s/

Nallaperumal Chidambaram
9/16/03 05:03:44 PM
CHEMIST

Kasturi Srinivasachar
9/16/03 05:18:06 PM
CHEMIST

Microbiology Review

This is Not Applicable.