CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-526

Administrative/Correspondence Reviews

13 PATENT INFORMATION

13.1 Patent Information, Section 505(b)

The following is provided in accordance with Section 505(b) of the Drug Price Competition and Patent Term Restoration Act of 1984.

Trade Name:	Ranexa™
Active Ingredient:	1-piperazineacetamide, *N*-(2,6-dimethylphenyl)-4-[hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)-
Strength:	500 mg and 375 mg
Dosage Form:	Oral tablets

13.2 Patent Information, 21 CFR 314.53(c)

Prior to August 2003, NDA sponsors were required under 21 CFR 314.53(c) to provide FDA with basic patent information in the form of a list. The original NDA 21-526, submitted on 27 December 2002, included a list of the following four patents:

4,567,264
6,303,607
6,369,062
6,479,496*

*Note: This patent was inadvertently listed as 6,479,946 in the original NDA, and a correction was submitted in an amendment dated 07 March 2003.

Subsequent to the original NDA, three other patents were cumulatively added to the list and submitted to the NDA on the following dates:

29 January 2003
6,503,911

07 March 2003
6,525,057

23 May 2003
6,562,826

For completeness and in accordance with the requirements that became effective in August 2003, newly-executed, completed Forms FDA 3542a for the seven patents listed above are provided in Section 13.2.1.

In accordance with the 21 CFR 314.53(c) requirements that became effective in August 2003, CVT submitted completed Forms FDA 3542a to NDA 21-526 for the following patents:

07 October 2003
6,617,328
6,620,814

28 February 2005
6,852,724

17 March 2005
6,864,258

For convenience, these completed forms are provided in Section 13.2.2. Upon review of these forms, corrections have been made to the claim listings for patents 6,620,814 (submitted on 07 October 2003) and 6,852,724 (submitted on 28 February 2005). These newly-executed, amended Forms FDA 3542a are provided in Section 13.2.3.

13.2.1 Patents Submitted Prior to August 2003

This section contains newly-executed, completed Forms FDA 3542a for the following patents submitted to NDA 21-526 before August 2003:

27 December 2002
- 4,567,264
- 6,303,607
- 6,369,062
- 6,479,496

29 January 2003
- 6,503,911

07 March 2003
- 6,525,057

23 May 2003
- 6,562,826

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-526

NAME OF APPLICANT / NDA HOLDER
CV Therapeutics, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Ranexa

ACTIVE INGREDIENT(S)	STRENGTH(S)
ranolazine, also known as 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)	375 and 500 mg

DOSAGE FORM
extended release tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
4,567,264	1/28/1986	5/18/2006

d. Name of Patent Owner	Address *(of Patent Owner)*	FAX Number *(if available)*
Syntex (USA) Inc (now Roche Palo Alto LLC)	3401 Hillview Ave City/State: Palo Alto, CA ZIP Code: 94304 Telephone Number: (650) 855-5311	(650) 855-5322 E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	FAX Number *(if available)*
Tricia Borga Suvari	3172 Porter Drive City/State: Palo Alto, CA ZIP Code: 94304 Telephone Number: (650) 384-8611	(650) 858-0388 E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☒ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

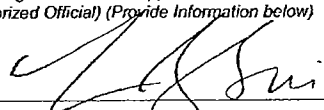
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

PSC Media Arts (301) 443-1090 EF

6. Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	6/13/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Tricia Borga Suvari, Vice President & General Counsel, Assistant Corporate Secretary CV Therapeutics, Inc.	
Address 3172 Porter Drive	City/State Palo Alto, CA
ZIP Code 94304	Telephone Number (650) 384-8611
FAX Number *(if available)* (650) 858-0388	E-Mail Address *(if available)*

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PSC Media Arts (301) 443-1090 EF

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-526

NAME OF APPLICANT / NDA HOLDER
CV Therapeutics, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Ranexa

ACTIVE INGREDIENT(S)	STRENGTH(S)
ranolazine, also known as 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)	375 and 500 mg

DOSAGE FORM
extended release tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,303,607	10/16/2001	5/27/2019

d. Name of Patent Owner	Address *(of Patent Owner)*	FAX Number *(if available)*
CV Therapeutics, Inc	3172 Porter Drive	
	City/State: Palo Alto, CA	
	ZIP Code: 94304	(650) 858-0388
	Telephone Number: (650) 384-8611	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	FAX Number *(if available)*
Tricia Borga Suvari	3172 Porter Drive	
	City/State: Palo Alto, CA	
	ZIP Code: 94304	(650) 858-0388
	Telephone Number: (650) 384-8611	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 1 (see additional pages for other claim)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

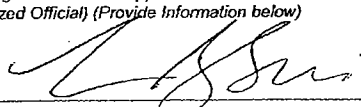
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	6/13/05

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☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Tricia Borga Suvari, Vice President & General Counsel, Assistant Corporate Secretary CV Therapeutics, Inc.	
Address 3172 Porter Drive	City/State Palo Alto, CA
ZIP Code 94304	Telephone Number (650) 384-8611
FAX Number *(if available)* (650) 858-0388	E-Mail Address *(if available)*

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PSC Media Arts (301) 443-1090 EF

Supplemental Page 1
FORM FDA 3542a (7/03)
Patent No. 6,303,607

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 2	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 6/13/05

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
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21-526

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TRADE NAME (OR PROPOSED TRADE NAME)
Ranexa

ACTIVE INGREDIENT(S)	STRENGTH(S)
ranolazine, also known as 1-piperazincacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)	375 and 500 mg

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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,369,062	4/29/2002	5/27/2019

d. Name of Patent Owner
CV Therapeutics, Inc and
Syntex (USA) Inc (now Roche Palo Alto LLC)

Address *(of Patent Owner)*
3172 Porter Drive (CVT)
3401 Hillview Ave (Syntex)

City/State
Palo Alto, CA

ZIP Code	FAX Number *(if available)*
94304	(650) 858-0388 (CVT)
Telephone Number	**E-Mail Address *(if available)***
(650) 384-8611 (CVT)	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ Tricia Borga Suvari

Address *(of agent or representative named in 1.e.)*
3172 Porter Drive

City/State
Palo Alto, CA

ZIP Code	FAX Number *(if available)*
94304	(650) 858-0388
Telephone Number	**E-Mail Address *(if available)***
(650) 384-8611	

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Patent Claim Number *(as listed in the patent)* — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. — Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

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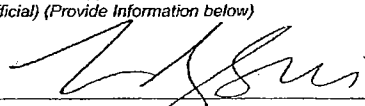
6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	6/13/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Tricia Borga Suvari, Vice President & General Counsel, Assistant Corporate Secretary CV Therapeutics, Inc.

Address	City/State
3172 Porter Drive	Palo Alto, CA
ZIP Code	**Telephone Number**
94304	(650) 384-8611
FAX Number *(if available)*	**E-Mail Address *(if available)***
(650) 858-0388	

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

ESC Media Arts (301) 443-1090 EF

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-526

NAME OF APPLICANT / NDA HOLDER
CV Therapeutics, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Ranexa

ACTIVE INGREDIENT(S)	STRENGTH(S)
ranolazine, also known as 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)	375 and 500 mg

DOSAGE FORM
extended release tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,479,496	11/12/2002	5/27/2019

d. Name of Patent Owner
CV Therapeutics, Inc

Address *(of Patent Owner)*
3172 Porter Drive

City/State
Palo Alto, CA

ZIP Code	FAX Number *(if available)*
94304	(650) 858-0388
Telephone Number	**E-Mail Address *(if available)***
(650) 384-8611	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Tricia Borga Suvari

Address *(of agent or representative named in 1.e.)*
3172 Porter Drive

City/State
Palo Alto, CA

ZIP Code	FAX Number *(if available)*
94304	(650) 858-0388
Telephone Number	**E-Mail Address *(if available)***
(650) 384-8611	

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

FORM FDA 3542a (7/03)

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 1 (see additional pages for other claims)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

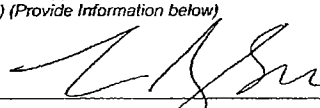
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	6/17/05

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Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
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Name
Tricia Borga Suvari, Vice President & General Counsel, Assistant Corporate Secretary CV Therapeutics, Inc.

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PSC Media Arts (301) 443-1090 EF

Supplemental Page 1
FORM FDA 3542a (7/03)
Patent No. 6,479,496

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 2	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

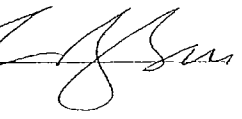
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 3	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 4	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: 

Date: 6/13/05

Supplemental Page 2
FORM FDA 3542a (7/03)
Patent No. 6,479,496

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 5	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 6	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 7	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

Signature: _____ Date: 6/13/05

Supplemental Page 3
FORM FDA 3542a (7/03)
Patent No. 6,479,496

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 8	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 9	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 10	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: [signature] Date: 6/13/05

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
21-526

NAME OF APPLICANT / NDA HOLDER
CV Therapeutics, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Ranexa

ACTIVE INGREDIENT(S)	STRENGTH(S)
ranolazine, also known as 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)	375 and 500 mg

DOSAGE FORM
extended release tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,503,911	1/7/2003	5/27/2019

d. Name of Patent Owner	Address *(of Patent Owner)*	
CV Therapeutics, Inc and Syntex (USA) Inc (now Roche Palo Alto LLC)	3172 Porter Drive (CVT) 3401 Hillview Ave (Syntex)	
	City/State Palo Alto, CA	
	ZIP Code 94304	FAX Number *(if available)* (650) 858-0388 (CVT)
	Telephone Number (650) 384-8611 (CVT)	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ Tricia Borga Suvari	3172 Porter Drive	
	City/State Palo Alto, CA	
	ZIP Code 94304	FAX Number *(if available)* (650) 858-0388
	Telephone Number (650) 384-8611	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Media Arts (301) 443-1099 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

PSC Media Arts (301) 443-1090 EF

6. Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	6/13/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Tricia Borga Suvari, Vice President & General Counsel, Assistant Corporate Secretary CV Therapeutics, Inc.

Address	City/State
3172 Porter Drive	Palo Alto, CA
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FAX Number *(if available)*	**E-Mail Address *(if available)***
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CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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FSC Media Arts (301) 443-1690 EF

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-526

NAME OF APPLICANT / NDA HOLDER
CV Therapeutics, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Ranexa

ACTIVE INGREDIENT(S)	STRENGTH(S)
ranolazine, also known as 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)	375 and 500 mg

DOSAGE FORM
extended release tablets

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Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,525,057	2/25/2003	5/27/2019

d. Name of Patent Owner
CV Therapeutics, Inc

Address *(of Patent Owner)*
3172 Porter Drive

City/State
Palo Alto, CA

ZIP Code	FAX Number *(if available)*
94304	(650) 858-0388
Telephone Number	**E-Mail Address *(if available)***
(650) 384-8611	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Tricia Borga Suvari

Address *(of agent or representative named in 1.e.)*
3172 Porter Drive

City/State
Palo Alto, CA

ZIP Code	FAX Number *(if available)*
94304	(650) 858-0388
Telephone Number	**E-Mail Address *(if available)***
(650) 384-8611	

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 1 (see additional pages for other claims)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

5. No Relevant Patents

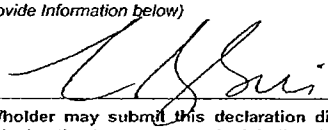
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

PSC Media Arts (301) 443-1090 EF

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	6/13/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/ holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Tricia Borga Suvari, Vice President & General Counsel, Assistant Corporate Secretary CV Therapeutics, Inc.	
Address 3172 Porter Drive	City/State Palo Alto, CA
ZIP Code 94304	Telephone Number (650) 384-8611
FAX Number *(if available)* (650) 858-0388	E-Mail Address *(if available)*

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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Supplemental Page 1
FORM FDA 3542a (7/03)
Patent No. 6,525,057

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 2	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 3	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 4	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 6/13/05

Supplemental Page 2
FORM FDA 3542a (7/03)
Patent No. 6,525,057

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 5	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 6	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 7	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 6/13/05

Supplemental Page 3
FORM FDA 3542a (7/03)
Patent No. 6,525,057

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 8	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 9	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 10	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 6/13/05

Supplemental Page 4
FORM FDA 3542a (7/03)
Patent No. 6,525,057

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 11	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 12	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 6/13/05

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-526

NAME OF APPLICANT / NDA HOLDER
CV Therapeutics, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Ranexa

ACTIVE INGREDIENT(S)	STRENGTH(S)
ranolazine, also known as 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)	375 and 500 mg

DOSAGE FORM
extended release tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,562,826	5/13/2003	5/27/2019

d. Name of Patent Owner	Address *(of Patent Owner)*	
CV Therapeutics, Inc	3172 Porter Drive	
	City/State: Palo Alto, CA	
	ZIP Code: 94304	FAX Number *(if available)*: (650) 858-0388
	Telephone Number: (650) 384-8611	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
Tricia Borga Suvari	3172 Porter Drive	
	City/State: Palo Alto, CA	
	ZIP Code: 94304	FAX Number *(if available)*: (650) 858-0388
	Telephone Number: (650) 384-8611	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 1 (see additional pages for other claims)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

5. No Relevant Patents

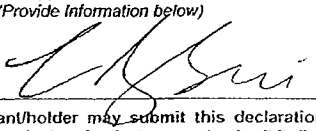
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

PSC Media Arts (301) 443-1090 EF

6 Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	6/13/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Tricia Borga Suvari, Vice President & General Counsel, Assistant Corporate Secretary CV Therapeutics, Inc.	
Address 3172 Porter Drive	City/State Palo Alto, CA
ZIP Code 94304	Telephone Number (650) 384-8611
FAX Number *(if available)* (650) 858-0388	E-Mail Address *(if available)*

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PSC Media Arts (301) 443-1090 EF

Supplemental Page 1
FORM FDA 3542a (7/03)
Patent No. 6,562,826

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 2	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 3	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 4	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 6/13/05

Supplemental Page 2
FORM FDA 3542a (7/03)
Patent No. 6,562,826

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 5	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificty the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 6	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 8	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 6/13/05

Supplemental Page 3
FORM FDA 3542a (7/03)
Patent No. 6,562,826

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 10	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 11	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 12	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

Signature: _____ Date: 6/13/05

Supplemental Page 4
FORM FDA 3542a (7/03)
Patent No. 6,562,826

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 13	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 14	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 15	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

Signature: _____ Date: 6/13/05

Supplemental Page 5
FORM FDA 3542a (7/03)
Patent No. 6,562,826

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 16	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 17	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 18	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 6/13/05

Supplemental Page 6
FORM FDA 3542a (7/03)
Patent No. 6,562,826

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 19	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 20	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 21	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 6/13/05

Supplemental Page 7
FORM FDA 3542a (7/03)
Patent No. 6,562,826

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 22	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 6/13/05

13.2.2 Patents Submitted After August 2003

This section contains copies of completed Forms FDA 3542a for the following patents that were previously submitted to NDA 21-526 after August 2003:

07 October 2003
6,617,328
6,620,814

28 February 2005
6,852,724

17 March 2005
6,864,258

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-526

NAME OF APPLICANT / NDA HOLDER
CV Therapeutics, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Ranexa

ACTIVE INGREDIENT(S)	STRENGTH(S)
ranolazine, also known as 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)-	375 and 500 mg

DOSAGE FORM
extended release tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,617,328	9/9/2003	5/27/2019

d. Name of Patent Owner
CV Therapeutics, Inc.
and
Syntex (U.S.A.) LLC

Address *(of Patent Owner)*
3172 Porter Drive

City/State
Palo Alto, CA

ZIP Code	FAX Number *(if available)*
94304	(650) 858-0388
Telephone Number	**E-Mail Address *(if available)***
(650) 384-8611	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ Tricia Borga Suvari

Address *(of agent or representative named in 1.e.)*
3172 Porter Drive

City/State
Palo Alto, CA

ZIP Code	FAX Number *(if available)*
94304	(650) 858-0388
Telephone Number	**E-Mail Address *(if available)***
(650) 384-8611	

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

FSC Media Arts (301) 443-1090 EF

6 Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	October 6, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Tricia Borga Suvari, Vice President & General Counsel, Assistant Corporate Secretary, CV Therapeutics, Inc.

Address	City/State
3172 Porter Drive	Palo Alto, CA
ZIP Code	**Telephone Number**
94304	(650) 384-8611
FAX Number *(if available)*	**E-Mail Address *(if available)***
(650) 858-0388	

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-526

NAME OF APPLICANT / NDA HOLDER
CV Therapeutics, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Ranexa

ACTIVE INGREDIENT(S)	STRENGTH(S)
ranolazine, also known as 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)-	375 and 500 mg

DOSAGE FORM
extended release tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,620,814	9/16/2003	5/27/2019

d. Name of Patent Owner
CV Therapeutics, Inc.

Address *(of Patent Owner)*
3172 Porter Drive

City/State
Palo Alto, CA

ZIP Code	FAX Number *(if available)*
94304	(650) 858-0388
Telephone Number	**E-Mail Address *(if available)***
(650) 384-8611	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ Tricia Borga Suvari

Address *(of agent or representative named in 1.e.)*
3172 Porter Drive

City/State
Palo Alto, CA

ZIP Code	FAX Number *(if available)*
94304	(650) 858-0388
Telephone Number	**E-Mail Address *(if available)***
(650) 384-8611	

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2 Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3 Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 1 (see additional pages for other claims)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

5 No Relevant Patents

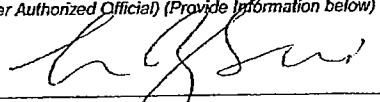
	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

FSC Media Arts (301) 443-1099 EF

6 Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	October 6, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Tricia Borga Suvari, Vice President & General Counsel, Assistant Corporate Secretary, CV Therapeutics, Inc.

Address	City/State
3172 Porter Drive	Palo Alto, CA
ZIP Code	**Telephone Number**
94304	(650) 384-8611
FAX Number *(if available)*	**E-Mail Address *(if available)***
(650) 858-0388	

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Supplemental Page 1
FORM FDA 3542a (7/03)
Patent No.: 6,620,814

4 Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 2	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4 Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 5	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4 Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	XYes ☐ No
4.2 Patent Claim Number (as listed in the patent) 6	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

Signature: _____ Date: October 6, 2003

Supplemental Page 2
FORM FDA 3542a (7/03)
Patent No.: 6,620,814

4. Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 7	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4. Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 9	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4. Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 11	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

Signature: _____ Date: October 6, 2003

Supplemental Page 3
FORM FDA 3542a (7/03)
Patent No.: 6,620,814

4 Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 14	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4 Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 15	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4 Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 16	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

Signature: _____ Date: October 6, 2003

Supplemental Page 4
FORM FDA 3542a (7/03)
Patent No.: 6,620,814

4 Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 17	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4 Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 18	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4 Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 19	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

Signature: _____ Date: October 6, 2007

Supplemental Page 5
FORM FDA 3542a (7/03)
Patent No.: 6,620,814

4. Methods of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 20	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4. Methods of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 21	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

Signature: _____ Date: October 6, 2003

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-526

NAME OF APPLICANT / NDA HOLDER
CV Therapeutics, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Ranexa

ACTIVE INGREDIENT(S)	STRENGTH(S)
ranolazine, also known as 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)	375 and 500 mg

DOSAGE FORM
extended release tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,852,724	2/8/2005	5/27/2019

d. Name of Patent Owner	Address *(of Patent Owner)*	
CV Therapeutics, Inc	3172 Porter Drive	
	City/State: Palo Alto, CA	
	ZIP Code: 94304	FAX Number *(if available)*: (650) 858-0388
	Telephone Number: (650) 384-8611	E-Mail Address *(if available)*:

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
Tricia Borga Suvari	3172 Porter Drive	
	City/State: Palo Alto, CA	
	ZIP Code: 94304	FAX Number *(if available)*: (650) 858-0388
	Telephone Number: (650) 384-8611	E-Mail Address *(if available)*:

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 1 (see additional pages for other claims)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	2/23/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Tricia Borga Suvari, Vice President & General Counsel, Assistant Corporate Secretary CV Therapeutics, Inc.

Address	City/State
3172 Porter Drive	Palo Alto, CA
ZIP Code	**Telephone Number**
94304	(650) 384-8611
FAX Number *(if available)*	**E-Mail Address *(if available)***
(650) 858-0388	

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PSC Media Arts (301) 443-1090 EF

Supplemental Page 2
FORM FDA 3542a (7/03)
Patent No. 6,852,724

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 2	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 5	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 6	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 2/23/05

Supplemental Page 2
FORM FDA 3542a (7/03)
Patent No. 6,852,724

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 12	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 13	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 13	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 2/23/05

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-526

NAME OF APPLICANT / NDA HOLDER
CV Therapeutics, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Ranexa

ACTIVE INGREDIENT(S)
ranolazine, also known as 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)

STRENGTH(S)
375 and 500 mg

DOSAGE FORM
extended release tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
6,864,258

b. Issue Date of Patent
3/8/2005

c. Expiration Date of Patent
5/27/2019

d. Name of Patent Owner
CV Therapeutics, Inc

Address *(of Patent Owner)*
3172 Porter Drive

City/State
Palo Alto, CA

ZIP Code
94304

FAX Number *(if available)*
(650) 858-0388

Telephone Number
(650) 384-8611

E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ Tricia Borga Suvari

Address *(of agent or representative named in 1.e.)*
3172 Porter Drive

City/State
Palo Alto, CA

ZIP Code
94304

FAX Number *(if available)*
(650) 858-0388

Telephone Number
(650) 384-8611

E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1050 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)*: 1 (see additional pages for other claims)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

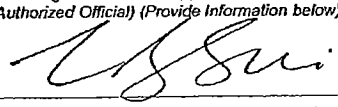
5. No Relevant Patents

	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6 Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	3/14/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Tricia Borga Suvari, Vice President & General Counsel, Assistant Corporate Secretary CV Therapeutics, Inc.	
Address 3172 Porter Drive	City/State Palo Alto, CA
ZIP Code 94304	Telephone Number (650) 384-8611
FAX Number *(if available)* (650) 858-0388	E-Mail Address *(if available)*

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PSC Media Arts (301) 443-1090 EF

Supplemental Page 1
FORM FDA 3542a (7/03)
Patent No. 6,864,258

4 Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 2	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

4 Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 3	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

4 Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 4	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

Signature: _____ Date: 3/14/05

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FORM FDA 3542a (7/03)
Patent No. 6,864,258

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 5	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 6	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 7	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 3/14/05

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Patent No. 6,864,258

4 Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 8	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4 Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 9	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4 Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 10	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 3/14/05

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FORM FDA 3542a (7/03)
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4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 11	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 12	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 13	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 3/14/05

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FORM FDA 3542a (7/03)
Patent No. 6,864,258

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 14	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 15	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 16	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 3/14/05

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FORM FDA 3542a (7/03)
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4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 17	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 18	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 19	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 3/14/05

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Patent No. 6,864,258

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 20	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 21	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 22	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

Signature: _____ Date: 3/14/05

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Patent No. 6,864,258

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 23	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 24	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 25	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 3/14/05

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4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 26	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 27	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 28	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 3/14/05

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4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 29	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 30	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

Signature: _____ Date: 3/14/05

13.2.3 Amended Forms FDA 3542a

This section contains newly-executed, amended Forms FDA 3542a for the following patents that were submitted to NDA 21-526:

6,620,814 (submission date: 07 October 2003)
6,852,724 (submission date: 28 February 2005)

These forms have been amended to correct claim listings.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-526

NAME OF APPLICANT / NDA HOLDER
CV Therapeutics, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Ranexa

ACTIVE INGREDIENT(S)	STRENGTH(S)
ranolazine, also known as 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)	375 and 500 mg

DOSAGE FORM
extended release tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,620,814	9/16/2003	5/27/2019

d. Name of Patent Owner
CV Therapeutics, Inc

Address *(of Patent Owner)*
3172 Porter Drive

City/State
Palo Alto, CA

ZIP Code	FAX Number *(if available)*
94304	(650) 858-0388
Telephone Number	**E-Mail Address *(if available)***
(650) 384-8611	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ Tricia Borga Suvari

Address *(of agent or representative named in 1.e.)*
3172 Porter Drive

City/State
Palo Alto, CA

ZIP Code	FAX Number *(if available)*
94304	(650) 858-0388
Telephone Number	**E-Mail Address *(if available)***
(650) 384-8611	

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)*: 1 (see additional pages for other claims)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

5. No Relevant Patents

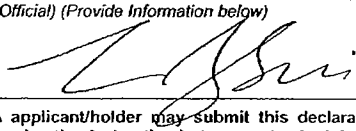
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

PSC Media Arts (301) 443-1090 EF

6. Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	6/13/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Tricia Borga Suvari, Vice President & General Counsel, Assistant Corporate Secretary CV Therapeutics, Inc.

Address	City/State
3172 Porter Drive	Palo Alto, CA
ZIP Code	**Telephone Number**
94304	(650) 384-8611
FAX Number *(if available)*	**E-Mail Address *(if available)***
(650) 858-0388	

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Supplemental Page 1
FORM FDA 3542a (7/03)
Patent No. 6,620,814

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 2	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 3	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 4	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 6/13/05

Supplemental Page 2
FORM FDA 3542a (7/03)
Patent No. 6,620,814

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 5	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 6	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 7	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 6/13/05

Supplemental Page 3
FORM FDA 3542a (7/03)
Patent No. 6,620,814

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 9	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 11	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 12	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 6/13/05

Supplemental Page 4
FORM FDA 3542a (7/03)
Patent No. 6,620,814

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 13	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 14	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 15	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 6/13/05

Supplemental Page 5
FORM FDA 3542a (7/03)
Patent No. 6,620,814

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 16	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 17	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 18	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

Signature: _____ Date: 6/13/05

Supplemental Page 6
FORM FDA 3542a (7/03)
Patent No. 6,620,814

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 19	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 20	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 21	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

Signature: _____ Date: 6/13/05

Supplemental Page 7
FORM FDA 3542a (7/03)
Patent No. 6,620,814

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 22	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 23	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 6/13/05

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-526

NAME OF APPLICANT / NDA HOLDER
CV Therapeutics, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Ranexa

ACTIVE INGREDIENT(S)	STRENGTH(S)
ranolazine, also known as 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)	375 and 500 mg

DOSAGE FORM
extended release tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,852,724	2/8/2005	5/27/2019

d. Name of Patent Owner	Address *(of Patent Owner)*	
CV Therapeutics, Inc	3172 Porter Drive	
	City/State: Palo Alto, CA	
	ZIP Code: 94304	FAX Number *(if available)*: (650) 858-0388
	Telephone Number: (650) 384-8611	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ Tricia Borga Suvari	3172 Porter Drive	
	City/State: Palo Alto, CA	
	ZIP Code: 94304	FAX Number *(if available)*: (650) 858-0388
	Telephone Number: (650) 384-8611	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☑ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 1 (see additional pages for other claims)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

5. No Relevant Patents

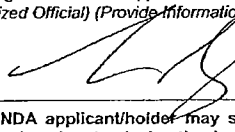
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

PSC Media Arts (301) 443-1090 EF

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	6/13/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Tricia Borga Suvari, Vice President & General Counsel, Assistant Corporate Secretary CV Therapeutics, Inc.	
Address 3172 Porter Drive	City/State Palo Alto, CA
ZIP Code 94304	Telephone Number (650) 384-8611
FAX Number *(if available)* (650) 858-0388	E-Mail Address *(if available)*

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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Supplemental Page 5
FORM FDA 3542a (7/03)
Patent No. 6,852,724

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 2	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 5	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 6	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina

Signature: _____ Date: 6/13/05

Supplemental Page 2
FORM FDA 3542a (7/03)
Patent No. 6,852,724

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 12	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 13	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 14	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* chronic angina	

Signature: _____ Date: 6/13/05

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-526

NAME OF APPLICANT / NDA HOLDER
CV Therapeutics, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Ranexa

ACTIVE INGREDIENT(S)	STRENGTH(S)
ranolazine, also known as 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)-	375 and 500 mg

DOSAGE FORM
extended release tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,617,328	9/9/2003	5/27/2019

d. Name of Patent Owner
CV Therapeutics, Inc.
and
Syntex (U.S.A.) LLC

Address *(of Patent Owner)*
3172 Porter Drive

City/State
Palo Alto, CA

ZIP Code	FAX Number *(if available)*
94304	(650) 858-0388
Telephone Number	**E-Mail Address *(if available)***
(650) 384-8611	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ Tricia Borga Suvari

Address *(of agent or representative named in 1.e.)*
3172 Porter Drive

City/State
Palo Alto, CA

ZIP Code	FAX Number *(if available)*
94304	(650) 858-0388
Telephone Number	**E-Mail Address *(if available)***
(650) 384-8611	

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

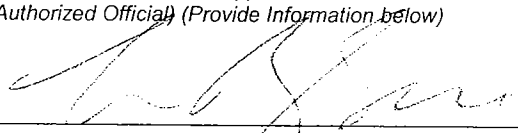
5. No Relevant Patents

	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	October 6, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Tricia Borga Suvari, Vice President & General Counsel, Assistant Corporate Secretary, CV Therapeutics, Inc.	
Address 3172 Porter Drive	City/State Palo Alto, CA
ZIP Code 94304	Telephone Number (650) 384-8611
FAX Number *(if available)* (650) 858-0388	E-Mail Address *(if available)*

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PSC Media Arts (301) 443-1090 EF

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-526

NAME OF APPLICANT / NDA HOLDER
CV Therapeutics, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Ranexa

ACTIVE INGREDIENT(S)	STRENGTH(S)
ranolazine, also known as 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)-	375 and 500 mg

DOSAGE FORM
extended release tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,620,814	9/16/2003	5/27/2019

d. Name of Patent Owner
CV Therapeutics, Inc.

Address *(of Patent Owner)*
3172 Porter Drive

City/State
Palo Alto, CA

ZIP Code	FAX Number *(if available)*
94304	(650) 858-0388
Telephone Number	**E-Mail Address *(if available)***
(650) 384-8611	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ Tricia Borga Suvari

Address *(of agent or representative named in 1.e.)*
3172 Porter Drive

City/State
Palo Alto, CA

ZIP Code	FAX Number *(if available)*
94304	(650) 858-0388
Telephone Number	**E-Mail Address *(if available)***
(650) 384-8611	

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No

2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No

2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No

3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

4.2 Patent Claim Number *(as listed in the patent)*: 1 (see additional pages for other claims)

Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

chronic angina

5. No Relevant Patents

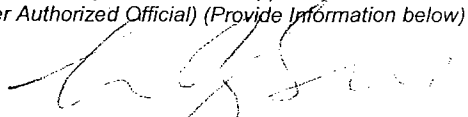
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

PSC Media Arts (301) 443-1090 EF

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	October 6, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Tricia Borga Suvari, Vice President & General Counsel, Assistant Corporate Secretary, CV Therapeutics, Inc.	
Address 3172 Porter Drive	City/State Palo Alto, CA
ZIP Code 94304	Telephone Number (650) 384-8611
FAX Number *(if available)* (650) 858-0388	E-Mail Address *(if available)*

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PSC Media Arts (301) 443-1090 EF

4. Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 2	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4. Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 5	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4. Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	XYes ☐ No
4.2 Patent Claim Number (as listed in the patent) 6	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

Signature: _____ Date: October 6, 2003

4. Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 7	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4. Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 9	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4. Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 11	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

Signature: _____ Date: Oct. 6 2003

4. Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 14	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4. Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 15	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4. Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 16	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

Signature: _____ Date: October 6, 2003

4. Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 17	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4. Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 18	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4. Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 19	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

Signature: _____ Date: October 6, 2003

4. Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 20	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

4. Methods of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 21	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) chronic angina

Signature: _____ Date: Oct 6, 2003

DEPARTMENT OF COMMERCE

National Oceanic and Atmospheric Administration

[I.D. 051203D]

Permits; Foreign Fishing

AGENCY: National Marine Fisheries Service (NMFS), National Oceanic and Atmospheric Administration (NOAA), Commerce.

ACTION: Notice of receipt of foreign fishing application.

SUMMARY: NMFS publishes for public review and comment a summary of an application submitted by the Government of the Russian Federation requesting authorization to conduct fishing operations in the U.S. Exclusive Economic Zone (EEZ) in 2003 under provisions of the Magnuson-Stevens Fishery Conservation and Management Act (Magnuson-Stevens Act).

ADDRESSES: Comments may be submitted to NMFS, Office of Sustainable Fisheries, International Fisheries Division, 1315 East-West Highway, Silver Spring, MD 20910; and/or to the Regional Fishery Management Councils listed here:

Paul J. Howard, Executive Director, New England Fishery Management Council, 50 Water Street, Mill 2, Newburyport, MA 01905, Phone (978) 465–0492, Fax (978) 465–3116;

Daniel T. Furlong, Executive Director, Mid-Atlantic Fishery Management Council, Federal Building, Room 2115, 300 South New Street, Dover, DE 19904, Phone (302) 674–2331, Fax (302) 674–4136.

FOR FURTHER INFORMATION CONTACT: Robert A. Dickinson, Office of Sustainable Fisheries, (301) 713–2276.

SUPPLEMENTARY INFORMATION: In accordance with a Memorandum of Understanding with the Secretary of State, NMFS publishes, for public review and comment, summaries of applications received by the Secretary of State requesting permits for foreign fishing vessels to fish in the U.S. EEZ under provisions of the Magnuson-Stevens Act (16 U.S.C. 1801 *et seq.*).

This notice concerns the receipt of an application from the Government of the Russian Federation requesting authorization to conduct joint venture (JV) operations in 2003 in the Northwest Atlantic Ocean for Atlantic mackerel and Atlantic herring. The factory ship DAURIYA is identified as the Russian vessel that would receive Atlantic mackerel and Atlantic herring from U.S. vessels in JV operations.

Dated: May 14, 2003.

Bruce C. Morehead,

Acting Director, Office of Sustainable Fisheries, National Marine Fisheries Service.

[FR Doc. 03–12739 Filed 5–20–03; 8:45 am]

BILLING CODE 3510–22–S

DEPARTMENT OF COMMERCE

Patent and Trademark Office

Grant of Interim Extension of the Term of U.S. Patent No. 4,567,264; Ranolazine

AGENCY: Patent and Trademark Office.

ACTION: Notice of interim patent term extension.

SUMMARY: The United States Patent and Trademark Office has issued a certificate under 35 U.S.C. 156(d)(5) for a one-year interim extension of the term of U.S. Patent No. 4,567,264.

FOR FURTHER INFORMATION CONTACT: Karin Ferriter by telephone at (703)306–3159; by mail marked to her attention and addressed to Mail Stop Patent Ext., Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313–1450; by fax marked to her attention at (703)872–9411, or by e-mail to *Karin.Ferriter@uspto.gov.*

SUPPLEMENTARY INFORMATION: Section 156 of title 35, United States Code, generally provides that the term of a patent may be extended for a period of up to five years if the patent claims a product, or a method of making or using a product, that has been subject to certain defined regulatory review, and that the patent may be extended for interim periods of up to a year if the regulatory review is anticipated to extend beyond the expiration date of the patent.

On March 5, 2003, patent owner Roche Palo Alto LLC, timely filed an application under 35 U.S.C. 156(d)(5) for an interim extension of the term of U.S. Patent No. 4,567,264. The patent claims the active ingredient ranolazine (Ranexa™). The application indicates that a New Drug Application for the human drug product ranolazine has been filed and is currently undergoing regulatory review before the Food and Drug Administration for permission to market or use the product commercially.

Review of the application indicates that, except for permission to market or use the product commercially, the subject patent would be eligible for an extension of the patent term under 35 U.S.C. 156. Since it is apparent that the regulatory review period will continue beyond the original expiration date of the patent (May 18, 2003), the term of the patent is extended under 35 U.S.C. 156(d)(5) for a term of one year, *i.e.*, until May 18, 2004.

Dated: May 9, 2003.

James E. Rogan,

Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office.

[FR Doc. 03–12729 Filed 5–20–03; 8:45 am]

BILLING CODE 3510–16–P

COMMITTEE FOR THE IMPLEMENTATION OF TEXTILE AGREEMENTS

Procedures for Considering Requests from the Public for Textile and Apparel Safeguard Actions on Imports from China

May 19, 2003.

AGENCY: The Committee for the Implementation of Textile Agreements (The Committee).

ACTION: Notice of Procedures

SUMMARY: This notice sets forth the procedures the Committee for the Implementation of Textile Agreements (the Committee) will follow in considering requests from the public for textile and apparel safeguard actions as provided for in the Report of the Working Party on the Accession of China to the World Trade Organization (the Accession Agreement). The Committee hereby notifies interested parties of the procedures it will follow in considering requests.

EFFECTIVE DATE: May 21, 2003.

ADDRESS: Request must be submitted to: the Chairman, Committee for the Implementation of Textile Agreements, Room H3100, U.S. Department of Commerce, 14th and Constitution Avenue, N.W., Washington, D.C. 20230. Ten copies of any such request must be provided.

FOR FURTHER INFORMATION CONTACT: William Dulka, Office of Textiles and Apparel, U.S. Department of Commerce, (202) 482-4058.

SUPPLEMENTARY INFORMATION:

Authority: Section 204 of the Agricultural Act of 1956, as amended (7 U.S.C. 1854); Executive Order 11651 of March 3, 1972, as amended.

BACKGROUND:

The Accession Agreement textile and apparel safeguard allows the United States and other World Trade Organization Member countries that believe imports of Chinese origin textile and apparel products are, due to market disruption, threatening to impede the orderly development of trade in these

13 PATENT INFORMATION

13.1 Patent Information, Section 505(b)

The following is provided in accordance with Section 505(b) of the Drug Price Competition and Patent Term Restoration Act of 1984.

Trade Name:	Ranexa™
Active Ingredient:	N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]piperazinyl}acetamide
Strength:	375 mg and 500 mg
Dosage Form:	oral tablets

13.2 Patent Information, 21 CFR 314.53(c)

As required under 21 CFR 314.53(c), the following information is provided:

Patent Number:	U.S. 4,567,264
Expiration Date:	May 18, 2003*
Type of Patent:	Drug substance
Name of Patent Owner:	Syntex (U.S.A.) Inc.

The undersigned declares that the above stated United States Patent Number U.S. 4,567,264 covers the drug substance of Ranexa™. This product is the subject of this application for which approval is being sought.

*An interim patent term extension application has been filed for this patent.

Patent Number:	U.S. 6,303,607
Expiration Date:	May 27, 2019
Type of Patent:	Method of use for treating angina
Name of Patent Owner:	CV Therapeutics, Inc.

The undersigned declares that the above stated United States Patent Number U.S. 6,303,607 covers a method of use of Ranexa™. This product is the subject of this application for which approval is being sought.

Patent Number: U.S. 6,369,062

Expiration Date: May 27, 2019

Type of Patent: Drug Product Formulation

Name of Patent Owner: CV Therapeutics, Inc.; Syntex (USA) Inc.

The undersigned declares that the above stated United States Patent Number U.S. 6,369,062 covers a formulation of Ranexa™. This product is the subject of this application for which approval is being sought.

Patent Number: U.S. 6,479,496

Expiration Date: May 27, 2019

Type of Patent: Method of use for treating angina

Name of Patent Owner: CV Therapeutics, Inc.

The undersigned declares that the above stated United States Patent Number U.S. 6,479,496 covers a method of use of Ranexa™. This product is the subject of this application for which approval is being sought.

Patent Number: U.S. 6,503,911

Expiration Date: May 27, 2019

Type of Patent: Drug Product Formulation

Name of Patent Owner: CV Therapeutics, Inc.; Syntex (USA) Inc.

The undersigned declares that the above stated United States Patent Number U.S. 6,503,911 covers a formulation of Ranexa™. This product is the subject of this application for which approval is being sought.

Patent Number:	U.S. 6,525,057
Expiration Date:	May 27, 2019
Type of Patent:	Method of use for treating angina
Name of Patent Owner:	CV Therapeutics, Inc.

The undersigned declares that the above stated United States Patent Number U.S. 6,525,057 covers a method of use of Ranexa™. This product is the subject of this application for which approval is being sought.

Tricia Borga Suvari
Vice President
General Counsel and Assistant Secretary
CV Therapeutics, Inc.

3/6/03
Date

EXCLUSIVITY SUMMARY

NDA # 21-526 SUPPL # HFD # 110

Trade Name Ranexa

Generic Name ranolazine

Applicant Name CV Therapeutics

Approval Date, If Known January 27, 2006

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

505(b)(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:

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 # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! 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 ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! 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:

Meg Pease-Fye, M.S.
Regulatory Health Project Manager
February 1, 2006

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

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

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

/s/

Margaret Pease-Fye
2/2/2006 07:27:44 AM

Norman Stockbridge
2/2/2006 07:32:49 AM

PEDIATRIC PAGE

NDA/BLA # : 21-526 **Supplement Type (e.g. SE5):** original **Supplement Number:** 000

Stamp Date: December 30, 2003 **Action Date:** October 30, 2003

HFD 110 **Trade and generic names/dosage form:** Ranexa (ranolazine) extended release 500 mg tablets

Applicant: CV Therapeutics **Therapeutic Class:**

Indication(s) previously approved: not applicable

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: treatment of chronic angina in patients who have not achieved an adequate response with other anti-anginal drugs

Is there a full waiver for this indication (check one)?

X **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

ction A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
X **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:**_____

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**_____

studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Meg Pease-Fye, M.S.
Regulatory Project Manager

cc: NDA 21-526
HFD-960/ Grace Carmouze

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/s/

Margaret Pease-Fye
2/1/2006 01:58:57 PM

16 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
Vice President, Regulatory Affairs
CV Therapeutics, Inc.

July 12, 2005
Date

16 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
Vice President, Regulatory Affairs
CV Therapeutics, Inc.

December 19, 2002
Date

Memorandum

To: ODEI Office Director

From: Robert Temple, MD

Date: January 27, 2006

Subject: NDA 21-526 (Ramoxa; ranolazine for angina)
Sponsor CV Therapeutics

Dr. Stockbridge's memo of January 22, 2006 captures most of the issues that led to an approvable action on ranolazine in 2003 and the resolution of them that leads to an approval action now. I will not address further CMC issues or effects on male fertility, but will consider effectiveness and several safety issues, notably QT effects and tumorigencity. In addition to Dr. Stockbridge's memo, I have made particular use for considering this NDA resubmission of Dr. Targum's review of ERICA (study 3037), dated 11/30/05 and her updated her review of safety and effectiveness, dated 12/8/05.

I. Effectiveness

In the previous action we considered R effective in the CARISA and MARISA studies, with exercise tolerance and angina rate endpoints, showing effects of about 30-35 msec at peak blood levels and 25-30 at trough and reductions in angina frequency of about 0.8-1.2 attacks per week. It should be noted that the relationship between effects on angina rate and exercise is not well established, except directionally. It seems entirely possible that people, faced with a particular task that can provoke angina, exercise until pain occurs, so that even a drug that increased exercise tolerance would not prevent most angina events. This might account for the quite modest effect on angina rates (reduction of about 1 event per week in CARISA) despite reasonable treadmill exercise effects of 30-35 sec, i.e., about what most anti-anginal drugs do.

This is relevant to the very small effect seen in ERICA (the study adding R to maximum amilodipine), just 0.2 (median) to 1 (mean) attack per week. This study, showing an effect in people on maximal amilodipine, is critical to our approval of R despite its QTc effect and variable plasma levels. The difference, in a large study, was statistically significant, but obviously small and one could question its value. For the reason indicated above, I believe the effect cannot be dismissed as trivial.

The consistently smaller effect of R in women needs to be noted in labeling.

II. Safety

A. General

As noted, the safety database for the ER product is modest, about 1000 patients, but with over 600 exposed for a year and almost 600 for more than two years. Dr. Targum's review of 12/8/05 updates

previous safety reviews. There is no suggestion of increased morality in controlled trials and the deaths seem consistent with expected causes in the angina population. Adverse effects are well-described in labeling and are more annoying than ominous, with more drop outs caused at the 0.5-1% level by dizziness, nausea, constipation, asthma and headache (vs essentially zero on placebo).

The small effect on serum creatinine (increase of 0.1mg/dl) seems of no consequence and is reversible (Dr. Stockbridge's memo says it is not but Dr. Hinderling's more recent analysis shows it is) and increase of creatinine to 2x baseline occurred in 0.3% of ranolazine and 1.2% of placebo patients (Targum, p 55).

B. QT prolongation

Ranolazine has not been the subject of a thorough QT study, but I agree with Dr. Stockbridge's conclusions that:

1. The mean QTc prolongation is modest, about 6 msec, and would not be a concern.

2. The QT effect is, however, plasma concentration-related and the PK of R is highly variable because of varying first pass effect. Thus, for plasma concentration in the upper 5% of patients given 1000 mg bid, the QTc effect is at least 15 msec, a value that is of some concern.

3. Use should be limited to people unresponsive to other therapy.

4. Labeling should strongly urge against excessive doses and concomitant therapy that could give higher blood levels.

5. The slope at the QTc/concentration curve appears higher (for unclear reasons) in patients with liver disease and R should not be used in them.

In a small study of PK effects of abnormal renal function, mild, moderate, and severe decreases in GFR all gave about a 40-50% increase in R blood levels. R is not renally excreted, so that this is very hard to explain, and is indeed implausible. Limited data on population PK does not seem to show increased plasma levels for mild impairment. At present, labeling needs to mention the increased blood level but the issue needs further evaluation. We will ask for a post-marketing commitment to examine complete population PK data and if still necessary, conduct of further PK study in patients with renal impairment.

C. Tumor promotion

Dr. Stockbridge described the published report indicating the R can promote intestinal cancer growth in a mouse model, indicating his belief that it needs to be in labeling and suggesting consideration of a Boxed Warning. I agree that it needs to be noted in labeling and in approved labeling it is presented as a Warning, but I do not believe it should be boxed, in agreement with Dr. Jacobs (memo 1/27/06) and Dr. Jacobson-Kram, because we know little about the clinical meaningfulness of such a finding, how familiar drugs behave in the assay, and how it relates to results agreement from conventional 2-year carinogenicity studies.

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/s/

Robert Temple
1/27/2006 11:50:20 AM
MEDICAL OFFICER

Memo to File:
NDA 21-526
January 24, 2006

The sponsor submitted rate-pressure product information from studies CVT 3033 and CVT 3031. Mean results are presented graphically below:

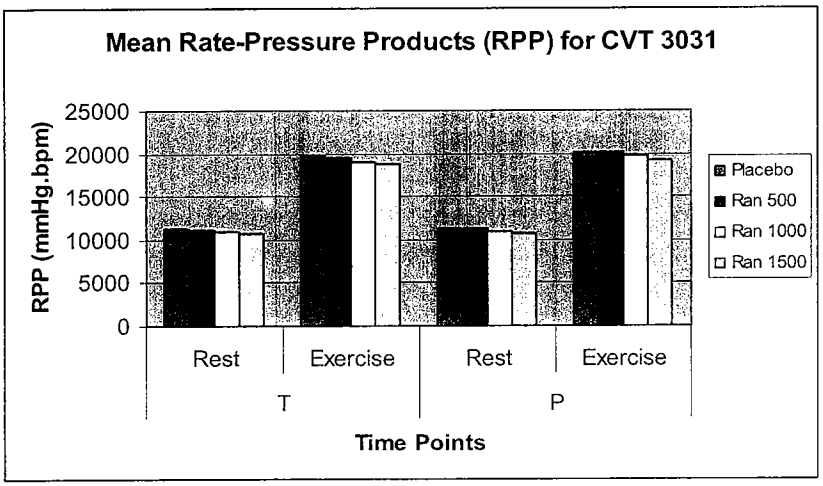

Figure 1. Mean rate-pressure products for CVT 3031 (T = trough, P=peak, Exercise =End of exercise).

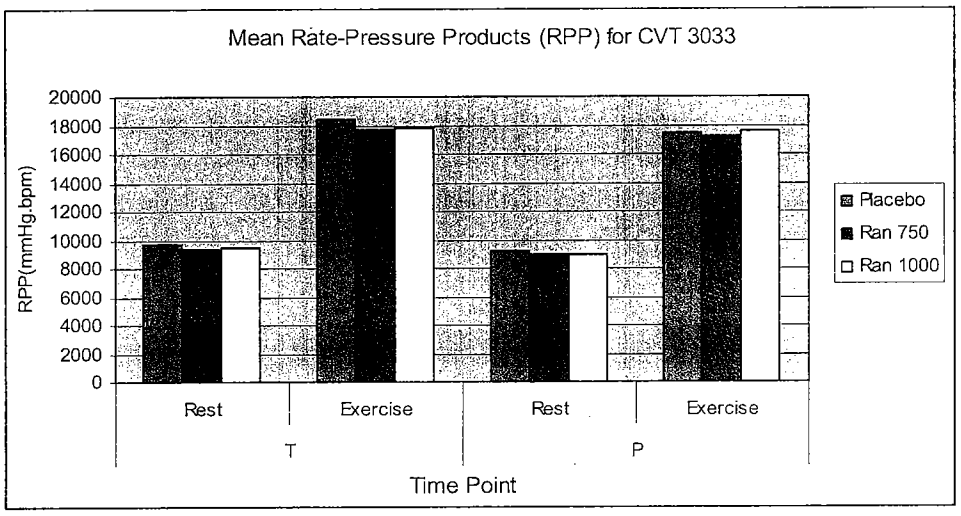

Figure 2. Mean rate-pressure products for CVT 3033 (T=trough, P=peak, Exercise = End of exercise).

Reviewer: In studies CVT 3033 and CVT 3031, ranolazine, compared to placebo, did not increase the rate-pressure product.

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/s/

Shari Targum
1/24/2006 04:55:47 PM
MEDICAL OFFICER

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

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

Sponsor: CV Therapeutics

Review date: 22 January 2006

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

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

This memo conveys the Division's recommendation for approval of ranolazine to treat patients with chronic stable angina despite other medical therapy.

NDA 21-526 (ranolazine for angina) was submitted 27 December 2002. It received an Approvable action on 30 October 2003. The rationale is captured in the Office Director's memo of the same date as follows:

- The safety database at relevant doses was much smaller than ICH guidelines.
- The dose-response relationship was poorly established[1].
- There was no thorough QT study.
- Testicular effects in rodents needed better characterization.
- The effects of combinations of metabolic inhibitors on exposure to inhibitors could result in much larger effects of ventricular repolarization.

All of these issues led to the idea that the easiest path to approval was a demonstration of effectiveness in a population with refractory angina, a position that was sustained by the Cardiac and Renal Drugs Advisory Committee in its deliberations of 9 December 2003.

Other summaries of the first cycle materials can be found in the secondary medical reviews by me (29 September 2003 and 7 November 2003) and the Divisional memo by Dr. Throckmorton (28 October 2003).

CMC issues

The chemistry and manufacturing review of Dr. Raman (16 December 2005) is focused on the 500-mg dose, since that is the only strength for which the sponsor is currently seeking marketing. Stability data support a 3-year expiry date.

Tradename issues

The Labeling and Nomenclature Committee and DDMAC recommended approval of the sponsor's proposed tradename, Ranexa, although these opinions will have to be updated before final approval.

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[1] *Indeed, the most compelling evidence of any such relationship comes from the clinical pharmacology reviewer's meta-analysis of exposure-response data from all clinical trials.*

Need for more safety and dose-response data

Revisiting the open issues enumerated in the Office Director's memo of 30 October 2003, I note that we agreed that the study in refractory patients would, for the purpose of supporting a claim in that population, satisfy the Agency's desire to see more safety data at a relevant dose. The Agency was willing to postpone acquisition of better dose-response data until there was a claim for use in a general angina population.

Anti-anginal effects on a background of amlodipine

In general, the sponsor, the Division, and the Office agreed to a single dispositive demonstration of effectiveness in a refractory population to support use in that setting. Drs. Targum (medical) and Freidlin (statistical) describe this study and its results in reviews dated 30 November 2005, 5 December 2005, and (safety update) 21 December 2005. Study CVT 3037 was a 6-week study in 565 mostly Eastern European patients with angina despite treatment with amlodipine 10 mg (and, in about 50% of cases, long-acting nitrates). Qualified subjects were randomized to placebo or to ranolazine 1000 mg BID, the most studied dose from the earlier development program. The primary end point was the angina rate, and there were some late alterations to the analysis plan to handle what turned out to be non-normally distributed data. By Dr. Freidlin's analysis, ranolazine reduced the median number of angina episodes per week by <10% (2.4 on placebo compared with 2.2 on ranolazine; p=0.03). There was a similar trend in the subgroup receiving long-acting nitrates. There was no trend among the 28% female subjects, recapitulating observations made in the earlier development program that ranolazine appears to be much less effective in women.

There was a patient-reported outcome secondary end point in CVT-3037, reviewed by William Pierce and Laurie Burke. They conclude that the Seattle Angina Questionnaire was an inadequately validated instrument, but it matters little. The only nominally significant result was on the component of angina frequency[2]. No effects were seen in components related to physical limitations, anginal stability, disease perception, or treatment satisfaction.

I do not know if a description of these findings is in a review yet, but Dr. Targum has assessed rate-pressure product information from two studies and there are no effects of treatment on rate-pressure product.

Effects on renal function

The clinical pharmacology and biopharmaceutics reviews of Drs. Hinderling and Bhattaram (11 October 2005 and 30 November 2005) address several open issues. Ranolazine has a small effect on serum creatinine and perhaps BUN. A new study in normal volunteers (301-16) did not show the effect on BUN (perhaps there is none), but it did show the expected 15% rise in serum creatinine and no effects on creatinine clearance or another measure of GFR, suggesting the mechanism to be inhibition of creatinine secretion. Reversibility has not been demonstrated.

Effects on male fertility

An earlier review by Dr. Hausner (29 January 2004) addressed the sponsor's response to concerns about decreased male fertility. The sponsor had testicular histopathology slides for dog (3 to 12 months) and rat (3 to 12 months) read by an external board-certified histopathologist. This external assessment found no evidence for a dose-related effect on the testes in either species.

---

[2] *Which is remarkable enough, considering the trivial change in median angina frequency.*

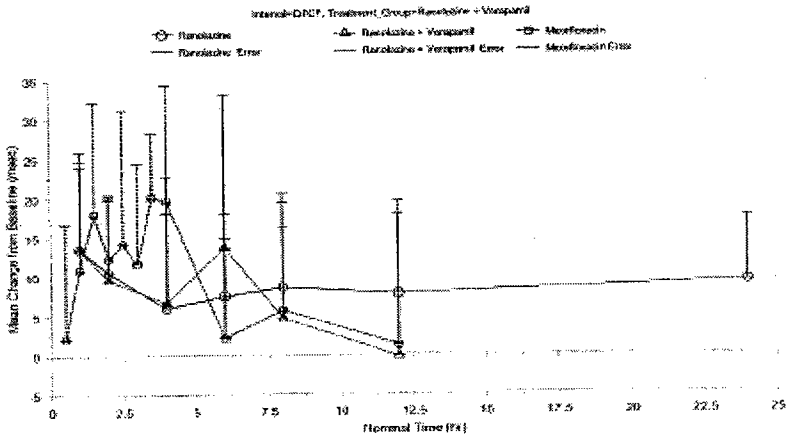
I consider that the open issue regarding testicular effects was resolved by lack of dose-related effects on testicular histology in the sponsor's 3- to 12-month studies in dogs and rats.

Effects on QTc...

A proper thorough QT study has not been performed, but I believe the information on hand is adequate.

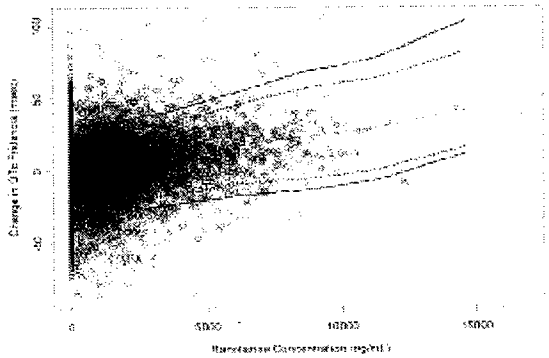
...with IV dosing and compared with moxifloxacin

Also reviewed is newly submitted study CVT 3112, a study of effects of IV ranolazine (at doses intended to produce exposure similar to that following 1000 mg PO), alone and in combination with diltiazem (90 mg BID) or verapamil (240 mg BID), compared with moxifloxacin 400 mg. The reviewers conclude that the effects of diltiazem and verapamil on exposure to ranolazine are less following IV than oral administration, probably because of the importance of first-pass effects. Nevertheless, the trial was potentially valuable for having an internal moxifloxacin contol, but the confidence limits are so wide (upper CI for moxifloxacin is more than 30 ms) that the study was, on the whole uninterpretable.



The above figure is from page 71 in Dr. Hinderling's review of 30 November 2005, ultimately derived from the verapamil interaction study. This is the only study I see with a moxifloxacin control. Note that the upper 95% CI for moxifloxacins effect is on the order of 25 ms, so high as to render the study inadequate as a "thorough QT study", if not completely uninterpretable.

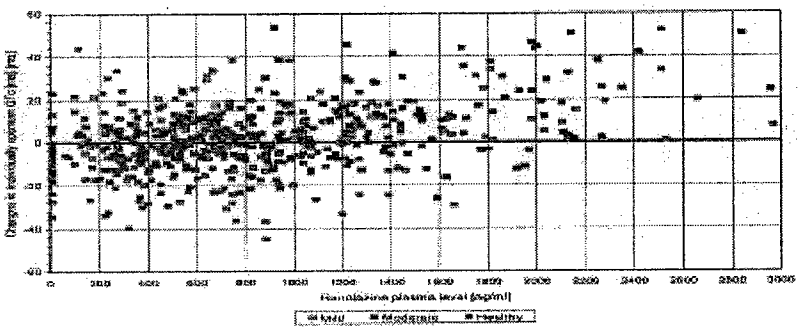
...in aggregate experience



The above figure is from page 404 of Dr. Hinderling's review of 11 October 2005 and is derived from an analysis of change from baseline in QTcF across all studies. The middle line has a slope of 2.3 ms/1000 ng/mL. Other than the hepatic impairment study, various component studies in the above analysis (see pages 123 and 139 for examples with oral dosing) are consistent.

...in patients with hepatic impairment

It had been previously noted that the relationship between exposure and QTc is steeper in patients with mild to moderate hepatic failure. The reviewers dismiss an analysis restricted to the one study that enrolled patients with hepatic impairment in favor of one based on the larger aggregate experience.



The figure above is from page 89 the review of Dr. Hinderling dated 30 November 2005 and an analysis of the hepatic impairment study done by Marek Malik. I am assured that comparison of linear exponential models, including an analysis of residuals, shows these data to be adequately fit by a linear model.

I have no idea why the relationship between plasma levels and QTc is different in patients with hepatic dysfunction.

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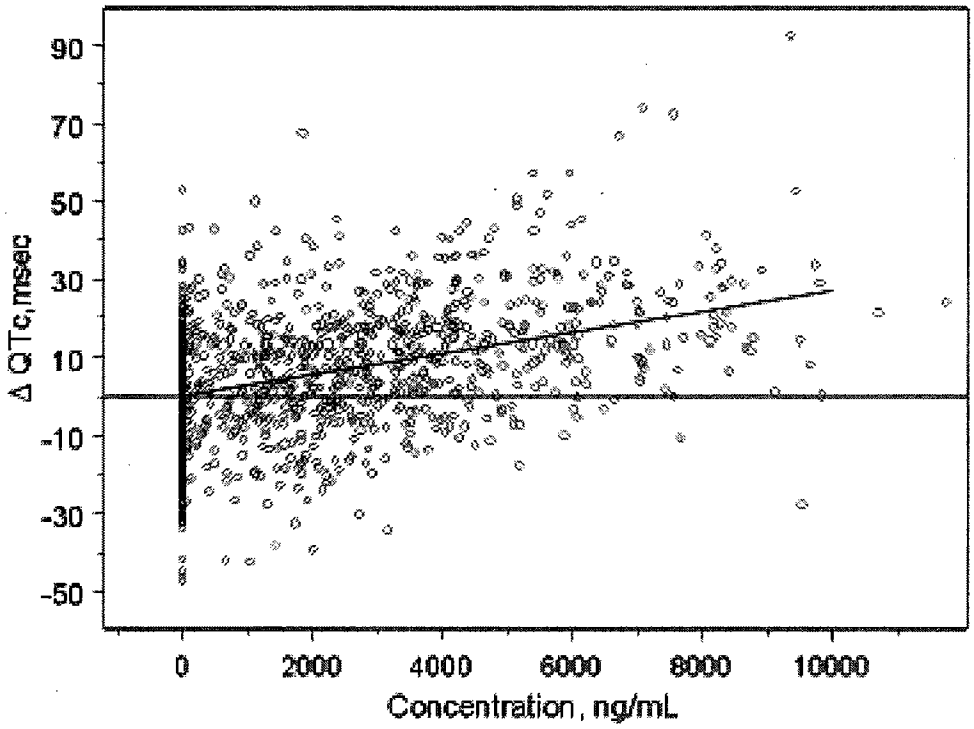
...with IV administration



The above figure is derived from one on page 417 of Dr. Hinderling's review of 11 October 2005 showing change in QTcF as a function of ranolazine level following IV administration. A line with a slope of 2.7 ng/mL has been added, and a linear model is probably adequate here, too.

...and the relationship to dose

What plasma levels are achieved by a given dose are quite variable. There is a modest non-linearity (higher than linear plasma levels with increasing dose) and moderate accumulation with repeated dosing. The PK results for Study CVT 3015 are shown below, but several other studies looked similar.

Dose	Day	Cmax	SD	Upper 95% CI for Cmax	Mean ΔQTcF[3]	Mean ΔQTcF at UCI for [ran][4]
500	1	1081	491	2043	2.5 ms	4.7 ms
	6	1766	1041	3806	4.1 ms	8.8 ms
1000	1	1955	1136	4182	4.5 ms	9.6 ms
	6	3825	1313	6399	8.8 ms	14.7 ms
1500	1	2721	1046	4771	6.3 ms	11.0 ms

[3] *Mean effect on QTcF is based on slope of 2.3 ms/1000 ng/mL*

[4] *Mean effect at the upper 95% CI for plasma level of ranolazine and slope of 2.3 ms/ng/mL. This is going to be a slight underestimate of the upper 95% CI for the effect on QT at this dose, because it takes no account of the CI for the slope.*

	6	6216	2662	11434	14.3 ms	26.3 ms

In the table above, I estimated the upper 95% CI for Cmax from the mean and SD. Estimated single-dose and repeated-dose effects on QTcF were estimated from the mean Cmax and the estimated slope of 2.3 ms/1000 ng/mL. The estimated effects at the upper 95% CI for Cmax are based on the same slope. Thus, chronic administration of ranolazine 1000 mg BID probably gives an effect on QTcF similar to that of a single 400-mg dose of moxifloxacin. Chronic administration of ranolazine at 1500 mg BID, or at 1000 mg BID with a modest 3A4 inhibitor) roughly doubles the effect compared with 1000 mg BID and no inhibitor.

Effects on tumor promotion

The preclinical reviews of Dr. Hausner (15 August 2005 and 6 December 2005) mainly concern the implications of a published report that ranolazine promotes the growth of intestinal cancer in a mouse model, at a dose providing exposure similar to human exposure in the treatment of angina. The report's authors predicted ranolazine to have this effect because it is thought to shift cells' metabolism to free fatty acids, enabling better energy extraction from the low-oxygen environment in the middle of a poorly perfused tumor. This is not a model system with which the Division or the Center's toxicologists have much experience. A consultant with the National Toxicology Program advised further study to confirm these results. Long-term rodent carcinogenicity studies are not optimal for detecting a cancer promoter, but Dr. Hausner's re-review of the 2-year studies provides some trends with regard to decreased survival in male mice and male rats and dose-related trends in some frequently seen rodent tumors (thyroid, adrenal, testes)[5].

If this is a real phenomenon and is applicable to humans, the people most at risk would be expected to be those with family or previous history of cancer or precancerous lesions—colonic polyps, smokers, benign prostatic hypertrophy, etc. There is no reason to expect that the mechanism would be specific to gastrointestinal tumors.

Summary

There is clearly an effect on QT at the only recommendable dose, and this effect is, in the absence of metabolic inhibitors, probably below the threshold of clinical concern. There is no good study with a positive control so I think it is difficult to be certain what the relative effects of ranolazine and, say, moxifloxacin on QT. The relationship between QT and plasma levels shows no sign of a plateau.

Since the benefits are small, the dose-response relationship for reducing angina frequency is poorly characterized, and nothing clearly limits dose, there will be some tendency for physicians to increase dose. Labeling should discourage increased exposure—higher doses or use in circumstances of impaired metabolism.

In addition, consideration should be given to a black box warning regarding the possibility of cancer promotion, until such time that the findings are refuted (results not replicable or idiosyncratic to one species or model system) or shown to be irrelevant (registry for clinical use). Some consideration should be given whether, if this finding were confirmed in relevance to man, a less than 10% reduction in angina frequency offsets this risk. I recognize that the tumor promotion study is not part of a standard

[5] *These findings were also noted in the original review. The Executive Carcinogenicity Assessment Committee has not revisited the 2-year studies, but they had previously concluded these studies lacked conclusive evidence of carcinogenicity. Dr. Targum also re-reviewed human long-term open-label safety data from the ranolazine development program. She found no obvious signals for increased cancers in humans, but there are no controlled long-term data.*

battery, and I do not recommend that it become standard. However, there was some rationale for employing it in this case, and I do not believe the results should be ignored. I find the results of the 2-year rodent carcinogenicity studies only moderately comforting.

In summary, I favor approval of Ranexa for patients with angina refractory to at least one other drug, presuming satisfactory labeling can be crafted.

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/s/

Norman Stockbridge
1/22/2006 07:50:48 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

10/12/05

NDA 21-526

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

Dear Ms. Karp:

We acknowledge receipt on July 27, 2005 of your July 26, 2005 resubmission to your new drug application for Ranexa (ranolazine) 375 and 500 mg Tablets.

We consider this a complete, class 2 response to our October 30, 2003, action letter for use in a refractory population. Therefore, the user fee goal date is January 27, 2006. However, we remind you that there are unresolved issues regarding approvability for use in the general population. Besides the safety concerns listed in our October 30, 2003 action letter regarding which you are conducting additional studies, you must also address the concern regarding tumor promotion in APC (Min/+) mice mentioned in our May 4, 2005 letter.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

If you have any question, please call:

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Norman Stockbridge
10/12/2005 08:50:17 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-526

INFORMATION REQUEST LETTER

5/4/05

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

Dear Ms. Karp:

Please refer to your December 27, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ranexa (ranolazine) extended release Tablets, 500mg.

We would like to bring to your attention the article cited below. Please incorporate your response to it in your complete response to the Approvable letter.

> Suckow MA et al. 2004. The anti-ischemic agent ranolazine promotes the development of intestinal tumors in APC(Min/+) mice. Cancer Letters 209:165-169.

If you have any questions, please call Meg Pease-Fye, Regulatory Project Manager, at (301) 594-5327.

Sincerely,

{See appended electronic signature page}

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

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/s/

Norman Stockbridge
5/4/05 11:01:40 AM

Minutes of a Teleconference

Meeting Date:	**December 2, 2005**
Application:	NDA 21-726 IND 43,735 Ranexa (ranolazine)
Sponsor:	CV Therapeutics
Type of Meeting:	**Internal discussion with outside consultants**
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Meeting Recorder:	Meg Pease-Fye, M.S.

FDA Participants:
Norman Stockbridge, M.D., Ph.D., Acting Director, Division of Cardiovascular and Renal Products
Ellis Unger, M.D., Deputy, Division of Cardiovascular and Renal Products
Thomas Marciniak, M.D., Team Leader, Medical Officers
Abraham Karkowsky, M.D., Ph.D., Team Leader, Medical Officers
David Jacobson-Kram, Ph.D. Associate Director, Pharmacology/Toxicology
Abigail Jacobs, Ph.D. Associate Director, Pharmacology/Toxicology
Albert Defelice, Ph.D., Team Leader, Pharmacology
Charles Resnick, Ph.D., Team Leader, Pharmacology
Elizabeth Hausner, D.V.M., Reviewer, Pharmacology
Donald Jensen, D.V.M., Reviewer, Pharmacology
Edward Fromm, R.Ph., Chief, Project Management Staff
Meg Pease-Fye, M.S., Regulatory Health Project Manager

Other Participants:
Mark Suckow D.V.M. Walther Cancer Center, University of Notre Dame
Nicholas Paoni Ph.D., Immusol, Incorporated, formerly of University of Notre Dame
John French Ph.D. Group Leader, Transgenic Carcinogenesis, National Institute of Environmental Health Sciences, National Institutes of Health

Background:
CV Therapeutics submitted an NDA to the Division in December, 2002 and received an approvable letter in October, 2003. A major amendment was submitted in July, 2005. The intended clinical population is for patients who have not achieved an adequate response with other anti-anginal drugs. The background for this meeting is well-documented in Dr. Hausner's review of 29 September, 2005 but is briefly repeated here:

On Thursday July 1, 2004, Division reviewer John Koerner, Ph.D. happened on the following article in a literature search conducted for other purposes:

> The anti-ischemia agent ranolazine promotes the development of intestinal tumors in APC(min/+) mice. M.A.Suckow, L.S. Gutieerrez, C.A. Risatti, W.R. Wolter, R.E. Taylor, M. Pollard, R.M. Navari, F.J. Castellino, N.F. Paoni. Cancer Letters 209(2004): 165-169.

The sponsor had not brought this article to Agency attention and had not included a reference to it in any submission. Although it was considered possible that CV Therapeutics was unaware of the publication, a telephone conversation with author Mark A. Suckow on July 1, 2004 informed the Division that the sponsor had been presented with a copy of the manuscript on July 29, 2003, prior to publication. Additional contact between the authors and CVT suggested that the sponsor recommended that the investigators used the dichloride salt form of ranolazine. Further, the material that the authors synthesized was offered to CV Therapeutics for analysis. CV Therapeutics declined, but viewed the results of the chemical analysis conducted by the sponsors and agreed that the material was acceptable. The purity was reported as [ ]. At the time of the discussion, the authors were still in possession of 25 grams of material.

Meeting:

Dr. Paoni described the background leading to this study: gene expression research identified ischemic muscle conditions affecting cardiac and skeletal muscles. Under hypoxic conditions, these muscles increasingly use glycolysis for energy production, instead of using fatty acid oxidation. This is supported by microarray and gene expression data as well as enzymatic and biochemical studies. Dr Paoni explained that he had tested ranolazine in this model based upon the proposed mechanism of modulation of fatty acid oxidation. Since tumors are relatively hypoxic and also use glycolytic metabolism, he hypothesized that inhibition of fatty acid oxidation would make the tumors more metabolically active and therefore more sensitive to chemotherapy, thereby enhancing their susceptibility to chemotherapeutic agents. In the mouse model used, ranolazine was associated with dysplastic adenomas and invasive carcinomas. Dr. Paoni said that CV Therapeutics acknowledged the receipt of the manuscript. The authors also offered CVT an opportunity for a new use (as an adjunct to cancer therapy).

The authors noted that there is no evidence to indicate than ranolazine is carcinogenic, but rather that it stimulated development of existing lesions. The product has had no effect in the wild type mice. There appears to be no species difference; guinea pigs, rats, dogs, rabbits, baboons and humans all use a modified metabolic pathway under hypoxic conditions. Three papers show that ranolazine works in the rat muscle, so Dr. Paoni believes that rodents can be used in the determination of how ranolazine leads to glycolysis during ischemia. Dr. Unger asked about the 5-flourouracil study using a subcutaneous transplant in nude mice. There was discussion regarding this 2 x 2 factorial trial, wherein animals received ranolazine alone, 5-FU alone, ranolazine plus 5-FU, or neither. Dr. Unger questioned whether the study showed a difference in tumor growth between the ranolazine group and the no treatment group, similar to the apparent effect observed in the published (min/+) mouse study. Dr. Paoni noted that there was a trend towards greater growth in the ranolazine group.

Dr. French noted that the trial tested only short-term exposure, and he concluded that, after having read the paper, the data do support promotion of pre-neoplastic lesions, although the APC(min/+) mouse model is a very sensitive and susceptible strain.

Dr. Stockbridge questioned the consultants regarding their level of concern in terms of patients who manifest no neoplastic disease, but who might be harboring an undiagnosed tumor (citing the example of slow growing prostate cancer). Dr. Paoni responded that if he were a cancer survivor, he would not take this drug. He suggested that patients be screened, or look for support of growth under hypoxic conditions. Dr. Stockbridge asked about benign prostatic hypertrophy or if smokers, reformed or otherwise, should take ranolazine. Dr. French emphasized the limitations of conclusions from the results of a single animal model/study, and suggested that the data should not be over-interpreted.

Dr. Stockbridge asked the consultants if they would recommend corroborative studies to confirm the mechanism. Dr. Paoni noted that this study has been performed twice, and the data had been pooled, with a resulting p-value < 0.01 for a drug-related effect. He feels quite confident about what these data show. The Agency asked forthrightly if these studies are usually tried in multiple animal models, using many compounds, and if results were only published when the drugs tested positive in one out of many models. Dr. Suckow stated that this is not the case.

When the Division asked how the ranolazine was synthesized, the authors noted that [redacted] manufactured their substance according to the information in CV Therapeutic's patent and the purity was determined to be > 99.6% as determined by nuclear magnetic resonance (NMR).

Dr. Defelice asked about the use of a hyperbaric chamber to test the enhanced glycolysis hypothesis of tumor promotion. The authors responded they did not give this consideration because they were trying to keep their studies close to therapeutic conditions.

Dr. Hausner asked the consultants about their opinion of this mouse model in terms of prediction and relevance to humans. Dr. French stated that this is indeed a useful model, adding there is a correlation between administration of carcinogenic agents and the induction of colon tumors. Further, he noted that dimethylhydrazine was used in a series of model (genetically susceptible) strains and CVT used outbred strains so they would not have observed the same results in the standard 2-year studies. Dr. French believes this assay should be repeated.

Dr. Paoni added that if repeated, it should be in a "well-characterized" model and recommended that the mice should not be allowed to reach end stage. Also, initial velocity of the kinetic stages of tumor promotion should be considered. Transgenic models were recommended. Dr. French agreed, noting several knock-out transgenic models that would permit latent tumors to be followed over the short-term. Dr. French indicated that he would provide a written review to CDER/FDA, which would have specific recommendations on how best to proceed

Date Minutes Drafted: December 13, 2005
Date Minutes Finalized: December 19, 2005

Signature minutes preparer: *{See appended electronic signature page}*
Meg Pease-Fye, M.S.

Concurrence, Chair: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

Reviewed:
N. Stockbridge 12/19/05
E. Unger 12.15.05
T. Marciniak 12/16/05
D. Jacobson-Kram 12.16.05
A. Jacobs 12.16.2005
A. Defelice 12.15.2005
E. Hausner 12.14.2005
E. Fromm 12.19.05

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/s/

Margaret Pease-Fye
12/20/2005 02:29:47 PM

Norman Stockbridge
12/20/2005 05:01:29 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Memo To File

DATE: November 28, 2005

SUBJECT: DMETS comments from trade name review sent to applicant

A. GENERAL COMMENTS

1. Increase the font size of the letters comprising the established name to at least half as large as the letters comprising the proprietary name. We refer you to 21 CFR 201.10(g)(2) for guidance.

2. Revise the established name using the same font size on all labels and labeling to read:

   ranolazine extended-release tablets

3. Relocate the net quantity so that it is not in close proximity to the product strength in order to avoid confusion between the two.

4. Revise the statement "Dosage Information" to read "Usual Dosage".

B. CONTAINER LABEL (60 COUNT)

1. Ensure that child resistant closures are used for bottles intended to be a "unit of use" (e.g. 60 capsules) to be in accordance with the Poison Prevention Act.

C. CONTAINER LABEL (500 COUNT)

1. Decrease the prominence (unbold) of the net quantity statement and relocate so it does not appear in conjunction with the product strength. Highlighting the net quantity "500" [redacted] container label may cause a selection error since the product is also available in a 500 mg tablet.

D. PACKAGE INSERT LABELING

1. See general comment A.1.

2. The How Supplied Section does not include [redacted] Please revise the How Supplied Section to include all dosage forms and strengths intended to be supplied.

IV. RECOMMENDATIONS

- DMETS has no objections to the use of the proprietary name, Ranexa™. This is considered a final decision. However, if the approval is delayed beyond 90 days from the signature of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

- DMETS recommends implementation of the container label, carton, and insert labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.

- DDMAC finds the proprietary name, Ranexa™, acceptable from a promotional perspective.

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/s/

Margaret Pease-Fye
11/28/2005 08:52:08 AM
CSO

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; WO22, M/S 4447)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #:** 05-0172
August 5, 2005	November 1, 2005	
DOCUMENT DATE:	**PDUFA DATE:**	
August 1, 2005	January 28, 2006	

TO: Norman Stockbridge, M.D.
Acting Director, Division of Cardiovascular and Renal Products
HFD-110

THROUGH: Meg Pease-Fye
Project Manager
HFD-110

PRODUCT NAME:	**NDA SPONSOR:** CV Therapeutics
Ranexa™ (Ranolazine Extended-release Tablets) 375 mg, 500 mg **NDA#:** 21-526	

SAFETY EVALUATOR: Tina M. Tezky, Pharm.D.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Ranexa™. This is considered a final decision. However, if the approval is delayed beyond 90 days from the signature of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the container label, carton, and insert labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name, Ranexa™, acceptable from a promotional perspective.

Denise P. Toyer, Pharm.D.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety

Carol Holquist, R.Ph.
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Division of Medication Errors and Technical Support
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Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; WO22, M/S 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 23, 2005

NDA#: 21-526

NAME OF DRUG: Ranexa™ (Ranolazine Extended-release Tablets)
375 mg, 500 mg

NDA HOLDER: CV Therapeutics

I. INTRODUCTION:

This consult was written in response to a request from the Division of Cardiovascular and Renal Products (HFD-110) for a re-review of the proprietary name, "Ranexa", regarding potential name confusion with other proprietary and/or established drug names. Revised container labels, cartons, and insert labeling were provided for review and comment.

The proprietary name, Ranexa, was previously reviewed by the Division of Medication Errors and Technical Support (DMETS) in July 2002 (see ODS consult #01-0071). At that time, DMETS had no objections to the use of the proprietary name Ranexa. Additionally, in May 2003 DMETS reviewed labels and labeling for Ranexa (see ODS consult #01-0071-1).

PRODUCT INFORMATION
Ranexa (ranolazine) is a partial inhibitor of fatty acid oxidation (pFOX inhibitor) that improves the efficiency of oxygen use by the ischemic cell. Ranexa is indicated for the treatment of chronic angina pectoris. The usual initial dose of Ranexa is 500 mg twice daily. Doses above 1000 mg twice daily offer little or no additional benefit and induce a greater rate of adverse reactions. Patients should be instructed to swallow the tablet whole, and not to bite or chew the tablet. Ranexa will be available as 375 mg and 500 mg extended-release tablets.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Ranexa to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The SAEGIS™ Online service [5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Ranexa. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have concerns with the name, Ranexa, in regard to promotional claims.

2. Since the July 2002 proprietary name review, the Expert Panel identified four additional proprietary names that were thought to have the potential for confusion with Ranexa. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

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[1] MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, Missouri.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.

[4] www location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS™ Online service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified for Ranexa

Product Name	Dosage form(s); Established name	Usual adult dose	Other*
Ranexa	Ranolazine Sustained Release Tablets 375 mg, 500 mg	500 mg by mouth twice daily	
Namenda Rx	Memantine Tablets 5 mg, 10 mg Memantine Oral Solution 2 mg/mL	Starting: 5 mg daily. Maintenance: 20 – 30 mg per day, in 2 to 3 divided doses.	LA
Zavesca Rx	Miglustat Capsules 100 mg	100 mg three times daily.	LA
Vanex-HD CIII	Phenylephrine, Chlorphenamine, and Hydrocodone Syrup 5 mg/2 mg/1.7 mg per 5 mL	2 teaspoonfuls 3-4 times a day, not to exceed 8 teaspoonfuls in 24 hours.	LA
Rhinaaxia Austria, Hungary, Switzerland, France, Belgium, Greece, Italy, Brazil	Magnesium Isospaglumate or Magnesium Spaglumate Nasal Spray	2 sprays in each nostril 5 times daily.	SA

*Frequently used, not all-inclusive.
**LA (look-alike), SA (sound-alike)

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Ranexa were discussed by the Expert Panel (EPD).

C. SAFETY EVALUATOR RISK ASSESSMENT

The products considered to have potential for name confusion with Ranexa are Namenda, Zavesca, Vanex, and Rhinaaxia. Upon further review of the names gathered from EPD, the name Rhinaaxia was not reviewed further because it is not marketed in the U.S., in addition to numerous differentiating product characteristics such as the product strength, dosage form, indication for use, and frequency of administration.

1. Namenda was identified as having look-alike potential with Ranexa. Namenda is indicated for the treatment of moderate to severe dementia of the Alzheimer's type and has also been used in the management of Parkinson's disease, dementia, organic psychosyndrome, neuroleptic drug-induced adverse reactions and spasticity. The usual starting oral dose of Namenda is 5 mg daily, increasing to a target maintenance dose of 20 – 30 mg per day, in divided doses. Namenda is available as 5 mg and 10 mg tablets and a 2 mg/mL oral solution. Namenda and Ranexa share three letters in similar positions (NAMENDA vs. RANEXA). The initial letters "N" vs. "R" and the third letters "M" vs. "N" have an orthographic similarity when scripted (see writing sample, page 5). However, the upstroke of the "D" in Namenda

provides an orthographic distinction between the two names. The two products share some product characteristics such as dosage form (tablet), route of administration (oral), frequency of administration (twice daily), and an overlapping numeral in dosage strength (5 mg vs. 500 mg). Although these similarities exist, both products are available in different strengths (5 mg and 10 mg tablets, 2 mg/mL oral solution vs. 375 mg, 500 mg). The indication of strength on a prescription will help alleviate the likelihood for confusion between these two products. DMETS believes the likelihood from confusion between Namenda and Ranexa is minimal.

Ranexa
Namenda

2. Zavesca and Ranexa may look-alike when scripted. Zavesca (miglustat) is indicated primarily for the treatment of mild to moderate type 1 (non-neuronopathic) Gaucher's disease in patients for whom enzyme replacement therapy is not an option. The usual dose is 100 mg three times daily. Zavesca and Ranexa share three letters in similar positions (ZAVESCA vs. RANEXA). The initial letters "Z" vs. "R" and the third letters "V" vs. "N" have an orthographic similarity when scripted (see sample below). In addition to the look-alike similarities, the two products share overlapping characteristics such as dosage form (tablets vs. capsules) and route of administration (oral). However the products differ with respect to frequency of administration (three times daily vs. twice daily). Additionally, the strength for Zavesca may be omitted on a prescription as it is only available in one strength; whereas, the strength for Ranexa will likely be indicated on a prescription as it is available in two different strengths (375 mg, 500 mg). DMETS believes the likelihood for confusion between Zavesca and Ranexa is minimal due to the aforementioned reasons.

Zavesca
ranexa

3. Vanex-HD was found to have look-alike potential with Ranexa, if the -HD is omitted from the name. Vanex-HD (phenylephrine/chlorphenamine/hydrocodone) is a schedule III controlled substance (CIII) indicated for the symptomatic relief of cough, nasal congestion, and discomfort associated with the common cold, sinusitis and acute upper respiratory tract infections. Vanex-HD is available as an oral syrup and the usual dose is 1 to 2 teaspoonfuls 3-4 times a day, not to exceed 8 teaspoonfuls in 24 hours. Vanex and Ranexa have the same four letters in similar positions (VANEX vs. RANEXA) which contribute to the look-alike characteristics of the two names. In addition, their initial letters ("V" vs. "R") may look similar when scripted (see sample below). However, the trailing "A" in Ranexa provides a visual distinction between the two names.

ranexa
Vanex

Vanex and Ranexa also share common characteristics such as route of administration (oral) and frequency of administration (three times daily). However, the strength for Vanex may be omitted on a prescription as it is only available in one strength; whereas, the strength for Ranexa will likely be indicated on a prescription as it is available in two different strengths (375 mg, 500 mg). DMETS believes the likelihood for confusion between Vanex-HD and Ranexa is minimal.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In review of the container label, carton and insert labeling of Ranexa, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement that may minimize potential user error.

A. GENERAL COMMENTS

1. We note the sponsor proposes a professional sample size of 60 tablets. DMETS believes this number is inappropriate for a physician sample. Sixty tablets represent a unit-of-use package size appropriate for a one month supply of medication.

2. Increase the font size of the letters comprising the established name to at least half as large as the letters comprising the proprietary name. We refer you to 21 CFR 201.10(g)(2) for guidance.

3. Revise the established name using the same font size on all labels and labeling to read:

   ranolazine extended-release tablets

4. Relocate the net quantity so that it is not in close proximity to the product strength in order to avoid confusion between the two.

5. Revise the statement "Dosage Information" to read "Usual Dosage".

B. CONTAINER LABEL (60 COUNT)

1. See general comments A.1 through 1.4.

2. Ensure that child resistant closures are used for bottles intended to be a "unit of use" (e.g. 60 capsules) to be in accordance with the Poison Prevention Act.

C. CONTAINER LABEL (500 COUNT)

1. See general comments A.1, A.2, and A.4.

2. Decrease the prominence (unbold) of the net quantity statement and relocate so it does not appear in conjunction with the product strength. Highlighting the net quantity "500" on the "375 mg" container label may cause a selection error since the product is also available in a 500 mg tablet.

D. PACKAGE INSERT LABELING

1. See general comment A.2.

2. The Precautions Section, Information for Patients Subsection is extensive and contains complex information that may be too comprehensive for patients to remember after discussion with their healthcare practitioner. As per CFR 201.57(e)(2) the full text of this information should be reprinted at the end of the package insert. This will enable patients to have access to this critical information after leaving the physician or pharmacy.

3. The How Supplied Section does not include the 375 mg dosage form. Please revise the How Supplied Section to include all dosage forms and strengths intended to be supplied.

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IV. RECOMMENDATIONS

A. DMETS has no objections to the use of the proprietary name, Ranexa™. This is considered a final decision. However, if the approval is delayed beyond 90 days from the signature of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the container label, carton, and insert labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.

C. DDMAC finds the proprietary name, Ranexa™, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-827-3242.

Tina M. Tezky, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph., M.S.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Tina Tezky
11/21/2005 04:25:38 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
11/22/2005 04:14:38 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
11/23/2005 11:29:23 AM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, Director, DMETS

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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Transmitted to FAX Number:	(650) 494 - 8769
Attention:	Ms. Carol Karp
Company Name:	CV Therapeutics
Phone:	(650) 384 - 8875
Subject:	Minutes from the **November 22, 2004** teleconference
Date:	11/30/04
Pages including this sheet:	5

From: **Meg Pease-Fye**
Phone: **301-594-5312**
Fax: **301-594-5494**

You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

PLEASE LET ME KNOW YOU RECEIVED THIS. THANK YOU!

Minutes of a Meeting

Meeting Date:	November 22, 2004
Application:	NDA 21-526 Ranexa (ranolazine) 375 and 500mg extended release Tablets
Sponsor:	CV Therapeutics
Type of Meeting:	B
Date Meeting Requested:	October 29, 2004
Date Confirmed:	November 3, 2004
Meeting. Package Rec'd:	November 4, 2004
Meeting Chair:	Thomas Marciniak, M.D.
Meeting Recorder:	Meg Pease-Fye, M.S.

FDA Participants:
Thomas Marciniak, M.D., HFD-110, Acting Deputy, Division of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D., Team Leader, Medical Officers, HFD-110
Shari Targum, M.D., Acting Team Leader, Medical Officers, HFD-110
Maryann Gordon, M.D., HFD-110, Medical Officer
Peter Hinderling, M.D., HFD-860, Reviewer, Clinical Pharmacology and Biopharmaceutics
Elizabeth Hausner, D.V.M., Reviewer, Pharmacology, HFD-110
John Koerner, Ph.D., Reviewer, Pharmacology, HFD-110
Valeria Freidlin, Ph.D., Reviewer, Statistics, HFD-710
Javher Advani, Ph.D., Reviewer, Chemistry, HFD-810
Meg Pease-Fye, M.S., HFD-110, Regulatory Health Project Manager

CV Therapeutics Participants:
Luiz Belardinelli, M.D., Senior Vice President, Pharmacology and Translational Biomedical Research
Brent Blackburn, Ph.D., Senior Vice President, Drug Discovery and Pre-clinical Development
Michael Burdick, Senior Director, Regulatory Affairs
Anne Champsaur, M.D., Executive Director, Drug Safety
Michael Crager, Ph.D., Senior Director, Biostatistics
Sandra Dixon, Ph.D., Principle Statistician
Heather Frazier, Ph.D., Scientist, Pharmacological Sciences
Carol D. Karp, Vice President, Regulatory Affairs
Anna Kunina, Associate Director, Statistical Programming
Lou Lange, M.D., Ph.D., Chairman and Chief Executive Officer
[redacted], Consultant
Dawn Parsell, Ph.D., Consultant
Alec Vardy, Senior Director, Clinical Data Management

Background:
Ranolazine SR is being developed for treatment of chronic angina. CV Therapeutics received an approvable letter for ranolazine on October 30, 2003, and on December 9, 2003 ranolazine went before the Cardio-Renal Advisory Committee where it was determined that CV Therapeutics needed to obtain additional clinical data in support of approval in a restricted population of

angina patients. A meeting was held on February 2, 2004 to discuss possible trial designs to obtain those data. On March 2, 2004, CVT submitted a Special Protocol Assessment (SPA) request (submission 223) entitled, "A Double-Blind, Randomized, Placebo-Controlled, Parallel Group Study of Ranolazine ER at a Dose of 1000 mg Twice a Day in Patients with Chronic Angina Who Remain Symptomatic Despite Concomitant Treatment with Amlodipine 10 mg Once a Day." The Division responded in writing on March 26, 2004. The objective of this meeting is to reach agreement on the format and content of the amendment to the NDA 21-526 based on the SPA. This amendment will be submitted as a complete response to the October 30, 2003 approvable letter.

Questions

1. Does the Agency agree with the content and format of the Integrated Summary of Efficacy proposed for the amendment?

Agency response: The Division finds this acceptable.

2. Does the Agency agree with the content and format of the Integrated Summary of Safety proposed for the amendment?

Agency response: The Division finds this acceptable.

3. Does the Agency agree with CVT's proposal to present Adverse Events (AE) data coded with the modified COSTART thesaurus used in the original NDA in the amendment and to convert coding of the AE data in the package insert to MedDRA at the time of final labeling discussions?

Agency response: The Division finds this acceptable.

4. Does the Agency agree with CVT's proposal to provide one combined item 8/10 to both the medical and statistical reviewers?

Agency response: The combination of clinical and statistical sections for the re-submission is acceptable to the Division.

5. Does the Agency agree with CVT's proposal to provide CRTs for the new studies CVT 3037, CVT 301-16 and CVT 3112 and updated CRTs for the long-term studies CVT 3032 and CVT 3034 in the same format that was used in the original NDA submission (based on CDISC version 2.0 standards)?

Agency response: The Division finds this acceptable.

6. Consistent with the original NDA submission, does the Agency agree with CVT's proposal to submit electronic copies of CRFs only for patients who died or discontinued due to AEs during the period covered by the amendment?

Agency response: The Division wants case report forms for serious adverse events as well. CVT asked if these forms should also be sent in for CVT 3032 and CVT 3034. Dr. Marciniak noted that as long as these are made available upon request, this is sufficient.

7. Does the Agency have any other comments on the content or format of the proposed amendment to the Ranexa NDA?

Agency response: Dr. Freidlin noted that for the secondary endpoints based on SAQ, the statistical analysis plan needs to provide more detail on when ANCOVA assumptions would be considered violated so that the Cochran-Mantel-Haenszel (CMH) test of mean scores would be used instead of ANCOVA. For example, the SAP should provide a specific normality test and a p-value level to declare a violation of normality and switch to the CMH test.

Dr. Advani noted that [redacted] stability data still needs to be submitted in order to determine expiry for ranolazine. CVT said they would submit this. Further CVT noted their intention to submit ~16 reports as an information amendment to the IND early in 2005.

Conclusions:
The Division agreed with CVT's proposed format and content of the amendment.

Date Minutes Drafted: November 22, 2004
Date Minutes Finalized: November 30, 2004

Signature minutes preparer: _____
Meg Pease-Fye, M.S.

Concurrence, Chair: _____
Thomas Marciniak, M.D.

Reviewed:
T. Marciniak 11/30/04
A. Karkowsky 11-30-04
S. Targum 11/29/04
M. Gordon 11-29-04
P. Hinderling 11/29/04
E. Hausner 11/29/04
V. Freidlin 11/29/04
J. Advani 11/24/04

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/s/

Thomas Marciniak
11/30/04 12:45:40 PM

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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Transmitted to FAX Number:	(650) 494 - 8769
Attention:	**Carol Karp**
Company Name:	C.V. Therapeutics
Phone:	(650) 384 - 8875
Subject:	Minutes from the April 16, 2004 meeting IND 43,735
Date:	5/6/04
Pages including this sheet:	6

From:	**Meg Pease-Fye**
Phone:	**301-594-5312**
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You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

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Minutes of a Meeting

Meeting Date:	April 16, 2004
Application:	NDA 21-526 IND 43,735 Ranexa (ranolazine) 375 and 500mg extended release Tablets
Sponsor:	CV Therapeutics
Type of Meeting:	C
Meeting requested:	March 22, 2004
Meeting Confirmed:	March 23, 2004
Mtg. Package Rec'd:	April 1, 2004
Meeting Chair:	Douglas C. Throckmorton, M.D.
Meeting Recorder:	Meg Pease-Fye

FDA Participants:
Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., HFD-110, Deputy, Division of Cardio-Renal Drug Products
Thomas Marciniak, M.D., HFD-110, Team Leader, Medical Officer
Shari Targum, M.D., HFD-110, Medical Officer
Katherine Lillie, M.D., HFD-110, Medical Officer
Peter Hinderling, M.D., HFD-860, Clinical Pharmacology and Biopharmaceutics Valeria Freidlin, Ph.D., HFD-710, Statistics
Meg Pease-Fye, HFD-110, Regulatory Health Project Manager

CV Therapeutics Participants:
Brent Blackburn, Ph.D., Senior Vice President, Drug Discovery and Pre-Clinical Development
Michael Burdick, Senior Director, Regulatory Affairs
Michael Crager, Ph.D., Senior Director, Biostatistics
Carol D. Karp, Vice President, Regulatory Affairs
Louis Lange, M.D., Ph.D., F.A.C.C, Chief Executive Officer and Chairman
Ewa Prokopczuk, M.D., Ph.D., Director, Clinical Research
Sandra Skettino, M.D., Vice President, Clinical Research and Operations
Whedy Wang, Ph.D., M.P.H., Executive Director, Biometrics
Andrew Wolff, M.D., F.A.C.C., Senior Vice President, Chief Medical Officer

TIMI Group:
Eugene Braunwald, M.D., Study Chair
David Morrow, M.D., M.P.H., Principal Investigator

Background:
Ranolazine is being developed for treatment of chronic angina. CV Therapeutics (CVT) received an approvable letter for ranolazine on October 30, 2003, and on December 9, 2003 ranolazine went before the Cardio-Renal Advisory Committee where it was determined that CV T needed to obtain additional clinical data in support of approval in a restricted population of angina patients. CVT met with the Division on February 6, 2004 to discuss their TIMI trial submitted to the IND on September 22, 2003. CVT requested this meeting to discuss pertinent issues concerning the trial and other outstanding issues.

Meeting
CVT wished to clarify outstanding issues prior to TIMI study discussions. First, they requested additional explanation about the outstanding issues surrounding the dosing scheme for the upcoming study. Dr. Throckmorton explained that to support the originally proposed claim for use in the general population, further definition of the dose-response relationship is necessary. If CVT were to develop data showing outcome benefits or utility in a refractory population, a lack of dose-response information would be less of an issue.

Dr. Throckmorton noted that while adverse events seemed to be more common at higher doses in CVT's angina trials, this increase did not translate into increased withdrawals at the higher doses, such that there remained a concern for dose-creep above the 750 mg to 1000 mg dose range. He reminded CVT that they should be looking to resolve all the outstanding issues:

- Safety: QT prolongation and syncope
- Dosing: response curve and events
- Concomitant use of nitrates and ketoconazole

He noted that if the sponsor's position was that drug-related effects on QTc did not herald a safety concern, that further studies should not prohibit use of CYP 3A4 inhibitors, and other drugs that affect plasma levels of ranolazine, such as diltiazem and verapamil.

Questions

1. **Does the Agency agree that if <u>no excess</u> mortality is associated with ranolazine treatment during this study, then these data will resolve any safety concerns related to the QT effect of ranolazine, and thus provide sufficient evidence to support the safety of long-term use of ranolazine as first line therapy for chronic angina patients?**

    a. **If the answer is yes, does the Agency agree that data from this study will resolve these QT concerns and provide sufficient evidence for the safety of long-term use of ranolazine as first line therapy for chronic angina patients even if statistical significance for the primary endpoint is not achieved?**

Agency response: The trial as it is proposed does not enroll patients at high enough risk, especially patients who would be taking drugs with likely metabolic interaction and may not provide sufficient reassurance. It is critical that patients at high risk for arrhythmias be enrolled and allowed to be exposed to concentrations of drug that are likely to be seen in general use. The Division looked at the proposed power of the study to exclude excess mortality. While there has been no clear agreement on what margin should be set there, the present study seems in line with what is necessary here.

    b. **If the answer is yes, does the Agency agree that data from this study will allow a reduction in cautionary language in the product labeling regarding the observation of QT prolongation with Ranexa?**

Agency response: If the study is altered to allow enrollment of patients who would be expected to take other medications that could increase their exposures to ranolazine, and the outcome is as proposed by the study, changes in labeling would be considered. There is clear precedent for

reducing the level of warnings in labeling as additional data become available (e.g., moxifloxacin).

2. **Does the Agency agree that if TIMI-36 meets its primary endpoint, that is, if the oral/IV ranolazine regimen is superior to placebo for reducing the rate of CV death, MI or recurrent ischemia during acute and subsequent long-term treatment of patients with non-ST elevation acute coronary syndrome receiving standard therapy, then this single study will enable an indication for this ranolazine regimen for treatment of non-ST elevation acute coronary syndromes and secondary prevention thereafter?**

Agency response: The Agency agreed; as long as the study goes to completion and as long as confirmatory evidence exists.

3. **Does the Agency agree that the proposed revisions to the exclusion criteria are appropriate?**

Agency response: No, the Agency does not agree. The December 2003 Cardio-Renal Advisory Committee was concerned that there was too little information about the effects in conjunction with use of long-acting nitrates. In addition, the Agency suggested concomitant use with 3A4 inhibitors as this would fit in well with CVT's hypothesis of "good QT" effect.

Dr. Throckmorton added a concern about the exclusion criteria for study 3037 potentially undermining the Agency's assurance of the safety of ranolazine. CVT's choice of exclusions were not to decrease the possibility of inducing QT prolongation, but rather that the potent 3A4 inhibitors can increase plasma levels of ranolazine 4-fold.

4. **As described in the draft protocol, a formal interim analysis is planned when 365 of the 730 major cardiovascular events (CV death, MI, severe recurrent ischemia) required to complete the trial have accrued. In the event the DSMB makes a recommendation to stop the study due to overwhelming evidence of positive benefit for ranolazine in terms of rate of CV death and MI ($p<0.001$), does the Agency agree that these data would resolve any safety concerns related to the QT effect of ranolazine, and thus provide sufficient evidence to support the safety of long-term use of ranolazine as first line therapy for chronic angina patients?**

Agency response: The Agency strongly cautions against stopping the study early at interim analysis, and suggested monitoring the aggregate event rate after 50% of events occurred on efficacy, as long as the study remains blinded. The statistical consequences of stopping the study early may leave CVT with not enough power to detect a meaningful effect on mortality, namely an effect at least as small as the one for which the study is nominally designed. CVT should plan on submitting a formal statistical plan to the Division for review.

5. **Does the Agency agree with CVT's proposal to not routinely submit expedited reports (IND Safety Reports) for the individual components of the composite primary endpoint used in the study: CV death, MI and recurrent ischemia?**

Agency response: This is acceptable to the Agency. A letter will be sent to CVT.

6. [ ]

Agency response: [ ]

7. Does the Agency have any concerns regarding the additional proposed changes to the TIMI-36 protocol?

Agency response: The Agency agrees with CVT's proposal to exclude digoxin and anti-arrhythmic drugs in this study.

8. Does the Agency have concerns regarding specific aspects of the study design or clinical evaluations?

Agency response: The Agency had no other comments at that time.

Conclusions

Agreements reached:

- All testicular toxicology issues from the approvable letter have been resolved.
- Reports of expected adverse events do not need to be submitted to the Agency.
- Exclusion of digoxin and anti-arrhythmic drugs from the study is acceptable.

Issues requiring further discussion:

- Dose response data
- Toleration and adverse events data

Action items:

- A letter will be sent to CVT waiving the required adverse event reporting to the Agency.
- CVT will submit a formal statistical plan for this study.
- CVT will submit simulations for CVT 3112 of the i.v. transition to oral dosing and a rationale for how CVT came up with the dose scheme.

Date Minutes Drafted: 4.27.04
Date Minutes Finalized: 5.03.04

Signature minutes preparer: _____
Meg Pease-Fye

Concurrence, Chair: _____

Douglas C. Throckmorton, M.D.

Reviewed:

D. Throckmorton	5/01/04
N. Stockbridge	4/30/04
T. Marciniak	4/28/04
S. Targum	4/28/04
P. Hinderling	4/28/04
V. Freidlin	4/27/04

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

/s/

Norman Stockbridge
5/6/04 09:43:36 AM

Minutes of a Meeting

Meeting Date:	February 6, 2004
Application:	NDA 21-526 Ranexa (ranolazine) 375 and 500mg extended release Tablets
Sponsor:	CV Therapeutics
Type of Meeting:	FDA request
Mtg. Package Rec'd:	January 23, 2004
Meeting Chair:	Robert Temple, M.D.
Meeting Recorder:	Meg Pease-Fye

FDA Participants:
Robert Temple, M.D., Director, Office of Drug Evaluation I
Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., HFD-110, Deputy, Division of Cardio-Renal Drug Products
Thomas Marciniak, M.D., HFD-110, Team Leader, Medical Officers
Maryann Gordon, M.D., HFD-110, Medical Officer
Katherine Lillie, M.D., HFD-110, Medical Officer
Karen Hicks, M.D., HFD-110, Medical Officer
Peter Hinderling, M.D., HFD-860, Reviewer, Clinical Pharmacology and Biopharmaceutics
Valeria Freidlin, Ph.D., Reviewer, Statistics
Zelda McDonald, HFD-110, Chief, Project Management Staff
Meg Pease-Fye, HFD-110, Regulatory Health Project Manager

CV Therapeutics Participants:
Brent Blackburn, Ph.D., Senior Vice President, Drug Discovery and Pre-clinical Development
Michael Burdick, Senior Director, Regulatory Affairs
Michael Crager, Ph.D., Senior Director, Biostatistics
Colin Hislop, M.D., Vice President, Clinical Research
I-Zu Huang, M.D., Director, Clinical Research
Markus Jerling, M.D., Ph.D., Vice President, Clinical Research
Carol D. Karp, Vice President, Regulatory Affairs
Lou Lange, M.D., Ph.D., F.A.C.C, Chief Executive Officer and Chairman
Sandra Skettino, M.D., Vice President, Clinical Research and Operations
Whedy Wang, M.P.H., Ph.D., Executive Director, Biometrics
Andrew Wolff, M.D., F.A.C.C., Senior Vice President, Chief Medical Officer

Background:
Ranolazine SR is being developed for treatment of chronic angina. CV Therapeutics received an approvable letter for ranolazine on October 30, 2003, and on December 9, 2003 ranolazine went before the Cardio-Renal Advisory Committee where it was determined that CV Therapeutics needed to obtain additional clinical data in support of approval in a restricted population of angina patients. This meeting was to discuss possible trial designs to obtain those data .

Meeting
The Agency opened the meeting by discussing the amount of additional trial data needed to obtain an approval in a restricted population, and agreed that a single trial was sufficient. In general, the sponsor has proposed trials in two restricted populations: those who remain

symptomatic after taking maximal approved doses of another agent and those who are intolerant of another class of anti-anginals (the latter can be because of documented intolerance or because their physician believes that it is unsafe to use that class based on the patient's medical condition). Either group could form the basis for an approval.

Questions and Discussion Points:

1. **Regarding the design of Study CVT 303X:**

   A. CVT intends to use rate of angina attacks as the primary efficacy endpoint. Does the FDA agree with this proposal?

Agency response: Both the Office and Division agreed that showing an add-on effect to a maximal dose of a drug in a single class, such as amlodipine, is sufficient and acceptable to the Agency. The rate of angina attacks is an acceptable endpoint, but Dr. Temple cautioned the sponsor that this had been a difficult endpoint to use in the past because of low angina rates, and he suggested they consider obtaining data on walk distance as well. The Agency agreed to a study powered on the basis of exercise results, and if there is a small p-value, the exercise endpoint would be sufficient. If the sponsor chooses to use co-primary endpoints, as they are likely to be correlated, Dr. Freidlin suggested using a closed testing procedure to test the co-primary endpoints.

B. If certain pre-specified enrollment criteria are met, CVT is considering performing an interim efficacy analysis through an independent data monitoring committee when 175 patients have completed the study. If the interim analysis is performed and is positive, CVT believes this should be sufficient to support initial approval of Ranexa. Does the FDA agree?

Agency response: The Agency strongly recommended that CVT reconsider performing an interim analysis. Drs. Temple and Throckmorton noted that problems that may occur:

- The angina events apparently present at an interim look might not stand up to scrutiny.
- Stopping is risky
- There is no urgency involved.

Dr. Temple added that CVT should not examine data un-blinded. He suggested CVT look at combined event rates during the study, possibly enlarging the study if rates are low.

C. Does the Agency agree with the statistical approach summarized in the statistical methods section of the study protocol outline?

Agency response: The Agency needs more detail before it can answer this question. Dr. Freidlin asked about the primary efficacy analysis and whether randomization would be adjusted for centers. If randomization is adjusted for centers, then the CMH test should be adjusted for centers too. Dr. Freidlin was concerned about small centers. CVT replied that they planned on pooling the centers by geographical region. CVT will submit more details, and schedule a teleconference with Statistics to discuss this issue.

D. CVT will aim to enroll patients at both US and non-US study centers. Enrollment at US centers may be substantially more difficult; therefore, the

majority of patients in this study may be recruited from Russia and other Eastern European countries. Would this be acceptable to the Agency?

Agency response: As long as the centers are available for inspection, the Agency agreed. Dr. Temple suggested CVT pay close attention to how studies are conducted outside the U.S. centers, as results often differ from U.S. centers.

2. If the primary endpoint of Study CVT 303X is met:

A. Would the data from this study alone be sufficient to support initial approval of Ranexa for patients who are resistant to treatment with other anti-anginal drugs, with or without the possible interim analysis?

Agency response: The proposed study supports the indication, but further discussions are needed in order to determine the best way to word the label to describe the patients who do not respond to other treatments. Dr. Throckmorton noted that part of the information obtained from this study is safety, particularly in terms of the characterization with long-acting nitrates and β-blockers.

B. A dose-titration approach based upon clinical response is currently described within the proposed Ranexa labeling. Combined with the additional data generated from Study CVT 303X, does this adequately address the dosing concerns described in the approvable letter?

Agency response: The Agency agreed the proposed dosing scheme is acceptable.

C. CVT will attempt to enroll as many women as possible into the study and will conduct exploratory subset analyses based on gender. Will this adequately address the gender issue described in the approvable letter?

Agency response: Dr. Throckmorton reminded CVT that the December 2003 Cardio-Renal Advisory Committee was concerned that there was too little information about the effects of ranolazine in women. CVT replied that they can show an improvement in women, just less than what is seen in men, supporting their argument that angina is the optimal endpoint. Dr. Throckmorton commented that any additional data will be useful in writing the label, as the more information provided within the label, the better.

3. If the primary endpoint is met, would Study CVT 303Y alone be sufficient to support expansion of the Ranexa labeling to include patients who are intolerant to treatment with other anti-anginal drugs, as described within the meeting package (p.7)?

Agency response: The target population for the CVT 303Y study is a combination of patients who are symptomatic on therapy (like in the first trial) and those who are intolerant of other therapies. Intolerance can also be in two forms: documented intolerance to a drug or class of drugs, and intolerance based on the physician's concerns about the use of a particular drug in a particular patient, or "physiologic intolerance." Dr. Throckmorton said that patients who have tried a drug and not tolerated it were clearly in need of new therapies. The case for physiologic intolerance is somewhat more difficult. Dr. Throckmorton believes physicians may exclude a large fraction of patients as likely to be intolerant when they are reminded that blood pressure decreases with the use of calcium channel blockers. In fact, however, intolerance on that basis

may be quite unusual. He was concerned about the possibility that most patients would be excluded based on expectation rather than on symptoms. If this is the population the sponsor chooses to study, the basis of their intolerance will need to be well described and defined for labeling.

Dr. Temple noted that he would expect that most patients in such a study will be on maximally tolerated doses of at least two drugs, but an effect when ranolazine is added to any drug would also be informative. The Agency took issue with the list of why patients might not be taking a β-blocker, indicating some were soft criteria, emphasizing the need for prior documentation of intolerance. CVT agreed to re-consider this list.

CV Therapeutics asked about the necessity of studying long-acting nitrates. Dr. Throckmorton replied that nitrates are a part of discussions about syncope. He suggested the inclusion of patients on patches to observe any effects.

4. If results from Study CVT 303Y become available before those from Study CVT 303X, could Study CVT 303Y alone be used to support initial approval of Ranexa in a restricted population of angina patients?

Agency response: The Agency said that CVT 303X is a more straightforward path, but obviously the Agency would look at the CVT303Y data if it were submitted.

5. Would Study CVT 303Z provide adequate additional safety exposure to support approval of Ranexa for the treatment of a general population of angina patients?

Agency response: The Agency was not certain that this trial would add meaningfully to what we already know about ranolazine, given its open-label nature.

Other discussion points:
CVT added that they intend to submit a Special Protocol Assessment to the Agency. The Agency said they would be happy to review such protocol.

CVT proposed using the Seattle questionnaire to look at patient symptoms. Dr. Throckmorton replied that as long as CVT submits an explanation and justifies its use and appropriateness in the population, it is acceptable. Currently, the Seattle questionnaire is being used with PCI.

The sponsor submitted a protocol for study #3036 MERLIN-TIMI to the IND (43,735) in September, 2003 and had asked to discuss this study in support of an acute coronary syndrome indication. The TIMI study would support an ACS indication, especially as related to atrial fibrillation. The proposed primary endpoints are cardiovascular death, myocardial infarction, or recurrent ischemia; there are four definitions of recurrent ischemia. The first three definitions,

1. Recurrent ischemia with ECG changes
2. Recurrent ischemia leading to hospitalizations
3. Recurrent ischemia prompting revascularization

are acceptable to the Agency; there was discussion about the fourth definition (Worsening angina/ischemia requiring additional therapy occurring after the day 14 visit), concluding that

CVT would take on risk if ranolazine was unable to beat placebo across the other classes of anti-anginal drugs. CVT responded that they do not want differential use of other drug classes to confound the data. Dr. Throckmorton believes the TIMI study is clear a route to an indication for the general population.

Questions in the TIMI submission:

1. Does the Agency agree that is Study CVT 3036 meets its primary endpoint, that is, if the intravenous/SR ranolazine regimen is superior to placebo for reducing the rate of CV death, MI or recurrent ischemia during acute and subsequent long-term treatment of patients with non-ST elevation acute coronary syndrome receiving standard therapy, then this single large study will enable an indication for this ranolazine regimen for treatment of non-ST elevation acute coronary syndrome and secondary prevention thereafter?

Agency response: This protocol would be assessing the risk of a therapy in a high-risk population. Assuming ranolazine succeeds on the primary endpoint in such a population (like dofetilide in DIAMOND-CHF), or even if it shows no toxicity then safety in a lower-risk population can be generally presumed. If this is the stated intent of the protocol, it is essential to enroll high-risk patients. The protocol, however, appears to exclude patients at high risk based on other diseases (hepatic or renal disease) and use of other medications. This should be reevaluated as patients at increased risk are what make this study so appealing. The Agency believes that CVT should change the exclusion criteria so there is a preference for open inclusion in order to understand the consequences of ranolazine therapy in high risk patients.

2. Does the Agency agree that if no excess mortality is associated with ranolazine treatment during this study, then these data will resolve any safety concerns related to the QT effect of ranolazine, and thus provide sufficient evidence to support the safety of long-term use of ranolazine SR as first line therapy for chronic angina patients? If yes, does the Agency agree that data from this study will resolve these QT concerns and provide sufficient evidence for the safety of long-term use of ranolazine SR as first line therapy for chronic angina patients even if statistical significance for the primary endpoint is not achieved?

Agency response: Dr. Throckmorton said that he thought the study certainly has the potential to support unrestricted use, as it is apparently designed to evaluate the safety consequences of ranolazine use in high-risk patients (as discussed above), potentially including the effects on arrhythmias.

3. Does the Agency have concerns regarding specific aspects of the study design or clinical evaluation?

Agency response: The Division would prefer to have a separate conversation to make certain everyone has a chance to review the protocol. CVT will follow up on patients that experienced a non-fatal primary event and these patients will stay in the study even though they may eventually die. The Agency agreed.

Dr. Hinderling noted that in the proposed TIMI study, the duration of the ranolazine infusion is considerably longer than in the previous studies with healthy volunteers. Dr. Throckmorton noted that the IV/oral switch concept is acceptable to the Agency. An evaluation of the PK of ranolazine is not planned in this study, but CVT has performed simulations. Dr. Hinderling asked

if the sponsor is making the assumption that the oral dose regimen of ranolazine used in patients with chronic stable angina is also the optimal dose regimen for patients with acute coronary syndrome; if this assumption is accepted, he believes, it follows that the plasma concentration profiles during the intravenous administration must be equivalent to the plasma concentration during oral treatment. The protocol of the present study in acute coronary syndrome patients adjusts the dose regimen during the IV and oral treatments phase for patients currently taking CYP 3A4 inhibitors, such as verapamil or diltiazem; however, the increased exposure to ranolazine in the presence of these 3A4 inhibitors during the IV and oral treatment administration may be different. Dr. Hinderling suggests an evaluation of the PK of ranolazine in the TIMI study.

4. Does the Agency have specific concerns regarding the planned statistical analyses?

Agency response: These concerns were raised in the discussions above.

Conclusions: It was agreed that both the TIMI study and CVT 303X may go forward. Further conversations with the reviewers are recommended.

Date Minutes Drafted: February 20, 2004
Date Minutes Finalized:

Signature minutes preparer: _____
Meg Pease-Fye

Concurrence, Chair: _____
Robert Temple, M.D.

Reviewed:

R. Temple	
D. Throckmorton	2/25/04
N. Stockbridge	2/24/04
T. Marciniak	2/23/04
M. Gordon	2-23-04
P. Hinderling	2/20/04
V. Freidlin	2/20/04
Z. McDonald	2/25/03

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/s/

Robert Temple
3/4/04 04:39:27 PM

********** -COMM. JOURNAL- ********** DATE DEC-11-2003 ***** TIME 10:03 *********

MODE = MEMORY TRANSMISSION START=DEC-11 10:02 END=DEC-11 10:03

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-FDA,CDER,OND,ODEI,DCRDP -

********** -CARDIO RENAL - ***** - 301 594 5494- **********

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Transmitted to FAX Number:	(650) 494 - 8769
Attention:	**Ms. Carol Karp**
Company Name:	CV Therapeutics
Phone:	(650) 384 - 8875
Subject:	Minutes from the November 25, 2003 teleconference
Date:	12/11/03
Pages including this sheet:	5

From: **Meg Pease-Fye**
Phone: **301-594-5312**
Fax: **301-594-5494**

You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

PLEASE LET ME KNOW YOU RECEIVED THIS. THANK YOU!

Minutes of a Teleconference

Date of teleconference:	November 25, 2003
Product:	Ranexa (ranolazine) 375 and 500mg Extended Release Tablets
Application:	NDA 21-526
Sponsor:	CV Therapeutics
Meeting Classification:	Type C
Purpose:	Guidance: To discuss issues relating to the Cardio-Renal Advisory Committee meeting on December 9, 2003

Attendees

Division of Cardio-Renal Drug Products

Douglas C. Throckmorton, M.D., Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D., Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D., Medical Team Leader, HFD-110
Valeria Freidlin, Ph.D., Statistician, Biometrics, HFD-710
Elizabeth Hausner, D.V.M., Pharmacology, HFD-110
John Koerner, Ph.D., Pharmacology, HFD-110
Atul Bhattaram, Ph.D., Clinical Pharmacology and Biopharmaceutics, HFD-860
Peter Hinderling, Ph.D., Clinical Pharmacology and Biopharmaceutics, HFD-860
Dornette Spell-Lesane, M.H.A., NP-C, Health Science Administrator, ACS, HFD-21
Meg Pease-Fye, Regulatory Health Project Manager, HFD-110

CV Therapeutics

Lou Lange, M.D., Ph.D., CEO and Chairman
Andrew Wolff, M.D., F.A.C.C., Senior Vice President, Clinical Research & Development
Carol D. Karp, Vice President, Regulatory Affairs
Margaret Dillon, Ph.D., Senior Director, Regulatory Affairs
Michael Burdick, Senior Director, Regulatory Affairs
Dawn Parsell, Ph.D., Regulatory Affairs Consultant
Donna Kato, Regulatory Affairs Consultant
Sandy Skettino, M.D., Vice President, Clinical Research & Operations
Colin Hislop, M.D., Vice President, Clinical Research
Markus Jerling, M.D., Ph.D., Vice President, Clinical Research
Michael Sweeney, M.B., F.R.C.P., Vice President, Medical Affairs
Ewa Prokopczuk, M.D., Director, Clinical Research
I-Zu Huang, M.D., Director, Clinical Research
Whedy Wang, M.P.H., Ph.D., Executive Director, Biometrics
Michael Crager, Ph.D., Senior Director, Biostatistics
Brent Blackburn, Ph.D., Senior Vice President, Drug Discovery and Preclinical Development
Luiz Bellardinelli, M.D., Vice President, Drug Discovery and Preclinical Development
Heather Fraser, Ph.D., Scientist, Drug Discovery and Preclinical Development
Kwan Leung, Ph.D., Senior Director, Preclinical Development
Scott Moren, Pharm.D, Manager, Medical Services

Background
Ranolazine SR is being developed for treatment of chronic angina. CV Therapeutics received an approvable letter for ranolazine on October 30, 2003. In a teleconference held on August 1, 2003, it was agreed that ranolazine would go before the Cardio-Renal Advisory Committee on December 9, 2003. The Agency requested this teleconference to discuss an outline for optimizing discussion during the meeting. The Division sent a copy of draft questions to be discussed at the Advisory Committee meeting to CV Therapeutics on November 24, 2003.

Telecon
Determination was made as to presentations to the Advisors and Consultant; CV Therapeutics will be making a brief presentation. The Division will not be making a presentation. Ms. Spell-Lesane explained that the agenda is set up to have general opening remarks and the presentation, followed by a question-and-answer period about the presentation, then a general discussion after which will be a break for lunch. After lunch there is time allotted for public comment and finally, discussion of the questions that the Division has written.

Dr. Throckmorton explained that during CV Therapeutics' presentation, they should expect interruptions as committee members may ask for clarification. He recommended they prepare a brief presentation with several back-up slides, and suggested that the presentation not exceed one-hour as it would best to optimize discussion time. He also encouraged CV Therapeutics not to present every possible argument, but try to tailor the discussion to highlight the most important points.

CV Therapeutics asked whether the committee members voted on every question, or if it was set up as an open-ended discussion. Dr. Throckmorton clarified that it will consist of mostly open-ended discussion, but that at the beginning of the meeting, he and the committee chair will determine the key question(s) necessitating a vote. At the point where a vote takes place, the chairman will stop the proceedings to take the vote.

CV Therapeutics asked when the draft questions become final. Dr. Throckmorton told them that they would have an opportunity to see the questions and correct any inconsistencies or raise issues. He further noted that the questions would not change significantly from those already drafted, emphasizing that the Division is looking for a useful meeting.

CV Therapeutics asked about question 3.1 and 3.2 where the term "second-line" was used. They requested that the word, "restricted" be substituted. The Division agreed. They asked for the removal of the term, "next steps" in favor of "toward approval." The Division declined. The Sponsor then asked about whether they should bring up their ideas about a large simple trial (TIMI). Dr. Throckmorton answered that this will likely come out discussion during question 2.4. Discussion will focus on what the Agency knows versus what it would like to know. Studies should be added to investigate non-anginal populations. Again, Dr. Throckmorton stated that the Division wants to give CV Therapeutics the best opportunity for a fair hearing.

Signature minutes preparer: _____
Meg Pease-Fye

Concurrence, Chair: _____
Douglas C. Throckmorton, M.D.

Drafted 11.26.03 Finaled 12.10.03

RD:

D Throckmorton	12.10.03
N Stockbridge	12.10.03
T Marciniak	12.10.03
E Hausner	12.03.03
J Koerner	12.03.03
A Bhattaram	12.02.03
P Hinderling	12.02.03
V. Freidlin	12.02.03
Z. McDonald	12.08.03

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

/s/

Margaret Pease-Fye
12/11/03 09:54:50 AM
Dr. Throckmorton signed off on these minutes on December 10, 2003 and they were faxed to the Applicant on the following day.

********** -COMM. JOURNAL- ********** DATE DEC-03-2003 ***** TIME 16:10 *********

MODE = MEMORY TRANSMISSION START=DEC-03 16:08 END=DEC-03 16:10

FILE NO.=883

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	#	916504948769	005/005	00:01:06

-FDA,CDER,OND,ODEI,DCRDP -

********** -CARDIO RENAL - ***** - 301 594 5494- **********

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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Transmitted to FAX Number:	(650) 494 - 8769
Attention:	**Ms. Carol Karp**
Company Name:	CV Therapeutics
Phone:	(650) 384 - 8875
Subject:	Minutes from the November 3, 2003 telecon
Date:	12/3/03
Pages including this sheet:	5

From: **Meg Pease-Fye**
Phone: **301-594-5312**
Fax: **301-594-5494**

You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

PLEASE LET ME KNOW YOU RECEIVED THIS. THANK YOU!

Minutes of a Teleconference

Date of teleconference:	November 3, 2003
Product:	Ranexa (ranolazine) 375 and 500mg Extended Release Tablets
Application:	NDA 21-526
Sponsor:	CV Therapeutics
Meeting Classification:	Type C
Purpose:	Guidance: To discuss issues relating to the Cardio-Renal Advisory Committee meeting on December 9, 2003

Attendees

Division of Cardio-Renal Drug Products
Douglas C. Throckmorton, M.D., Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D., Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D., Medical Team Leader, HFD-110
Shari Targum, M.D., Medical Officer, HFD-110
Maryann Gordon, M.D., Medical Officer, HFD-110
Elizabeth Hausner, D.V.M., Pharmacology, HFD-110
John Koerner, Ph.D., Pharmacology, HFD-110
Atul Bhattaram, Ph.D., Clinical Pharmacology and Biopharmaceutics, HFD-860
Nhi Nguyen, Pharm.D., Clinical Pharmacology and Biopharmaceutics, HFD-860
Joga Gobburu, Ph.D., Clinical Pharmacology and Biopharmaceutics, HFD-860
Nallaperumal Chidambaram, Ph.D., Chemistry, HFD-810
Zelda McDonald, Chief, Project Management Staff, HFD-110
Meg Pease-Fye, Regulatory Health Project Manager, HFD-110

CV Therapeutics
Brent Blackburn, Ph.D., Senior Vice President, Drug Discovery and Pre-clinical Research
Michael Crager, Ph.D., Senior Director, Biostatistics
Margaret Dillon, Ph.D., Senior Director, Regulatory Affairs
Colin Hislop, M.D., Vice President, Clinical Research
I-zu Huang, M.D., Director, Clinical Research
Markus Jerling, M.D., Ph.D., Vice President, Clinical Research
Carol D. Karp, Vice President, Regulatory Affairs
Kwan Leung, Ph.D., Senior Director, Pre-clinical Development
Louis Lange, M.D., Ph.D., Chairman and Chief Executive Officer
[ ] Toxicology Consultant
Ewa Prokopczuk, M.D., Director, Clinical Research
Sandra Skettino, M.D., Vice President, Clinical Research and Operations
Michael Sweeney, M.B., F.R.C.P., Vice President, Medical Affairs
Wedy Wang, M.P.H., Ph.D., Executive Director, Biometrics
Andrew Wolff, M.D., F.A.C.C., Senior Vice President, Clinical Research and Development

Background

Ranolazine SR is being developed for treatment of chronic angina. CV Therapeutics received an approvable letter for ranolazine on October 30, 2003. In a teleconference held on August 1, 2003, it was

agreed that ranolazine would go before the Cardio-Renal Advisory Committee on December 9, 2003. The Agency requested this teleconference to discuss an outline for optimizing discussion during the meeting.

Telecon

Dr. Throckmorton identified the dates for fully redacted packages (containing no proprietary secrets) to be submitted to the Advisors and Consultants. CV Therapeutic's package is due on November 5, 2003 and the Division's package is due on November 7, 2003. He emphasized that all documents will be made public and will be put on the web 24 to 48 hours prior to the meeting. Drs. Targum and Stockbridge are drafting questions to discuss at the meeting. The draft questions will be shared with CV Therapeutics in order to clarify data, so a useful discussion may occur, avoiding arguments about data discrepancies. Dr. Throckmorton asked CV Therapeutics if they had any questions to ask the reviewers.

CV Therapeutics suggested going through the issues identified in the approvable letter. First, they asked what the Division's thinking was with respect to the QTc values, specifically the mean maximal increases of 2-5 msec with doses of 500 to 1000 mg. Dr. Throckmorton stated the concern is that CV Therapeutics calculated the mean population excluding patients with hepatic impairment and those receiving concomitant medications, thereby underestimating the probable 'population' effects of ranolazine on QTc. He asked if the drug interaction information was also excluded, and CV Therapeutics acknowledged that it was. Dr Throckmorton noted that CV Therapeutics estimates are seen as underestimating the population mean maximum change in QTc. He also said that the Agency's pharmacometrics reviewers constructed a concentration-QTc change model, concluding that the slope for the hepatically impaired is about twice as that for normals. Dr. Throckmorton clarified that he was concerned with the possibility of having a patient with hepatic impairment taking ranolazine along with diltiazem and ketoconazole, and what their effects on QT would be. He believes that CV Therapeutics should focus on those issues instead of only focusing on chosen doses of drug.

The Agency's pharmacometrics reviewers had concluded that there is a linear relationship between QT prolongation and the concentration of ranolazine. CV Therapeutics responded that it was hard to explore the limits of patients' toleration. Patients were unable to be titrated up to 15,000 ng/ml. Then 8000 ng/ml was chosen because it calculated out to 20 milliseconds (something of a benchmark). Of the patients that reached 8000 ng/ml, about half had symptoms including syncope, hypotension and dizziness. Fewer than 1% were able to achieve plasma concentrations of 8000 ng/ml and still be asymptomatic.

CV Therapeutics commented that in their hepatic studies, there was a steeper concentration – QTc slope in patients with hepatic impairment compared to healthy volunteers. Also, they do not know if QT is more pronounced with other drugs as they were unable to find literature on other drugs. CV Therapeutics then asked if there is a number used to characterize QT. Dr. Throckmorton responded that, no, there is no single number, and ranolazine demonstrates no evidence of a plateau. Dr. Throckmorton reiterated that the Agency is focusing on concentration versus effect, not on the concentration versus dose relationship.

Next, CV Therapeutics referred to the statement in the approvable letter with respect to the number of patients given relevant doses, and asked for a clarification of relevant dose. Dr. Throckmorton said that comes from ICH guidelines that say data needs to be provided for 1000 patients treated for at least one month at 750 to 1000 mg b.i.d. CV Therapeutics responded that they have data on fewer than 400 patients on a t.i.d dosing; but they also have data on 813 patients on sustained release ranolazine for 80 days, and on 910 patients for more than one month. Dr. Throckmorton acknowledged that they have provided enough information to address this issue.

CV Therapeutics noted that Dr. Temple had requested data concerning patients in controlled studies, but most of their patients (not quite 90%) were in long-term open label studies with doses at ~750 mg. They began open label studies after RAN 3033 and the majority of their data represents doses at 750 to 1000 mg. Dr. Throckmorton asked if they have submitted a safety update, and they replied that they had. Dr. Throckmorton suggested that they summarize where the data came from and to what extent their information satisfies what the Agency is requesting. CV Therapeutics suggested creating a table and asked if the Division would need it before the deadline for submitting the Advisory Committee briefing documents. Dr. Throckmorton encouraged this table to be submitted to the Division in order for the Division to write questions for the Advisory Committee.

CV Therapeutics asked for clarification about whether they would need to show additional benefit in populations not adequately treated with maximally-tolerated or labeled doses of more than one class of approved anti-anginals or could they study just one other approved anti-anginal. Dr. Throckmorton said he would clarify this with Dr. Temple and would get back with them, but that he also understood Dr. Temple had been speaking of benefit on top of a single other class of anti-anginals.

CV asked about the phrase in the approvable letter, "demonstration of a benefit on fixed clinical endpoints." They asked specifically if a trial should be designed to show non-inferiority, that ranolazine is not worse than placebo. Dr. Throckmorton responded that such a trial would not have to be placebo-controlled. He suggested a trial with ranolazine versus a β-blockersuch as atenolol noting it would be better if ranolazine could be shown to beat an active comparator, but the Agency would consider a non-inferiority trial.

CV Therapeutics asked about the large study with the TIMI group. They asked that if there was no increase in mortality, would that allay the Agency's concerns or would they need a large simple trial studying ranolazine versus a CCB (e.g. amlodipine)? Dr. Throckmorton replied that details matter more than usually because the Division is concerned about an intermittent event (torsade). It is hard to conclude there will be no adverse effect just because none is seen in a trial. The development program for tilithromycin assessed the efficacy of the drug but also captured rare adverse events. Although there was modest data obtained in that program, Dr. Throckmorton suggested such a development program as a possible path.

Dr. Lange from CV Therapeutics asked how the Agency was looking at the QT data, specifically what the Agency thinks about the non-clinical data from models evaluating pro-arrhythmic risk, for example, the isolated canine ventricular wedge preparation. Dr. Throckmorton answered that the models were interesting; however he had concluded that details in the non-clinical data undermined CV Therapeutics' own argument. He believes that there is reason for concern when using the wedge prep. Dr. Koerner added that the data are inconclusive; the data are generally consistent with QT prolongation, and some of the data suggests pro-arrhythmic risk. Additionally, the Agency does not know the sensitivity or the specificity of these models. Therefore a clear decision cannot be made regarding pro-arrhythmic risk based on these models. CV Therapeutics remarked that they would welcome an opportunity to discuss these models, specifically what parts of the data the Agency considers inconclusive. They do not understand which data suggests a QT prolongation. Dr. Throckmorton replied that the pharmacology/toxicology reviews would be included in the package going to the Advisors and Consultants, and that CV Therapeutics would have an opportunity to review their comments. He also noted that further conversations with the pharmacology reviewers would be appropriate.

CV Therapeutics asked if there were other concerns not listed in the letter. Dr. Throckmorton suggested they consider arguments for justifying their proposed dosing regimen. The Agency believes that the recommended doses are not well characterized and that the 750 and 1000 mg dose effects were indistinguishable. Dr. Throckmorton suggested that this is another issue to discuss at the Advisory

Committee meeting. He suggested CV Therapeutics prepare a proposal on how to dose that can be discussed before the Advisory Committee. CV Therapeutics replied that they were considering 500 mg and 750 mg as a maximal dose.

CV Therapeutics asked why their September 13, 2003 submission that addressed 3, 6 and 12-month toxicity studies was still considered inadequate with regard to addressing the Division's concerns about ranolazine's effect on fertility. Dr. Hausner said her concerns involved male fertility at high doses, that provided only low multiples of human exposure. She commented that there were no specifications or methods provided concerning fixation, preparation and analysis of tissues. Dr. Throckmorton said he believes that for testicular injury, a certain level of analysis is expected, and the Agency was not assured that this was addressed in available data. Dr. Throckmorton noted that this issue has not been resolved, and would be better to have more discussion on the topic prior to bringing it up to the Advisory Committee.

The final safety concern involved the nature of adverse events that occurred in the Phase 3 trial. Symptoms observed included dizziness, syncope and palpitations, occurring in what appeared to be dose-dependent fashion. CV Therapeutics attributed those effects to the α-adrenergic blocking effect of ranolazine. They acknowledged that there is a CNS effect at very high concentrations of ranolazine. Dr. Throckmorton advised CV Therapeutics to provide a rationale for why this finding is not of concern, since this may also come up in the Advisory Committee meeting.

CV Therapeutics asked if they could propose a trial in the background package for the Advisory Committee to consider, and also asked if the Committee meeting would be a whole or half day.

Dr. Throckmorton said the meeting would be the whole second day. He said it would be okay to include a proposal for a trial. The Committee would discuss the type of trial, not the "right" trial.

Action items

1. Ms. Pease-Fye will set up opportunities for CV Therapeutics to have conversations with reviewers as necessary.
2. CV Therapeutics will submit the table discussed above in time for the Division to write the questions.
3. The draft questions will be forwarded to CV Therapeutics as soon as they are available.

Signature minutes preparer: Meg Pease-Fye 12.2.03
Meg Pease-Fye

Concurrence, Chair: 12.3.03
Douglas C. Throckmorton, M.D.

Drafted 11.10.03 Finaled

RD:

D Throckmorton	12.02.03	J Koerner	11.24.03
N Stockbridge	12.01.03	A Bhattaram	11.17.03
T Marciniak	12.01.03	N Nguyen	11.17.03
S Targum	12.01.03	J Gobburu	11.19.03
M Gordon	11.24.03	N Chidambaram	11.17.03
E Hausner	11.24.03	Z McDonald	12.02.03

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 30, 2003

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Ranolazine – NDA 21-526

TO: Director, Division of Cardio-Renal Drug Products, HFD-110

The principal identified problems in our letter are the rat infertility/testicular histopathology problem and a substantial effect on QT/QTc that does not seem outweighed by any documented advantage over available treatment. I believe there are other problems too.

1. Safety

   The safety data base is very small for a chronically used drug. My calculation from the safety review is that of 749 patients who received the SR form (the IR data are almost all at doses too low to be pertinent), 217 received it for less than one month, leaving just 532 people with more than one month at a relevant dose. That is not close to ICH E-1 and I can think of no good reason for that unless the case can be made that there is urgent need for the drug to treat refractory angina. We may need, of course, to see what we said at EOP2, if that is an issue, but these data are really not enough. I would expect that the additional study they'll need in refractory patients (parallel design, everyone on maximal anti-anginal Rx, doses of 500, 750, 1000, 1500 mg b.i.d., with, say, 75 per group) might be enough. They do seem to have accumulated adequate long term data, but I note the survival curve on Dr. Gordon's page 52. Do we believe that would be typical for an angina population?

2. Dose-response and how to use the drug

   The highly variable plasma concentrations and the many factors that can influence it pose significant difficulties for finding a D/R. C/R is actually easier in such cases and perhaps modeling efforts already have given us this, but there needs to be some way to dose safely and effectively. (Titration no doubt will be the way, but how do you really do that? If we were clear on what doses give what range of blood levels, perhaps doses beyond some point would be done only with ECG.) The closest to adequate D/R study had just one week treatment periods (making tolerability very hard to assess) and seems to be at least a little different from the 12 week study (3033). Note also that D/R would be quite different with and without diltiazem or verapamil. In any case, I think another dose response study is needed (it can be the add-on study we're already seeking):

   - Parallel design
   - Doses of 500, 750, 1000, 1500 b.i.d. unless that latter is clearly not tolerated (or is too risky – QT wise)
   - At least 4 weeks
   - In people on maximal anti-anginal regimen, perhaps a mixture of DHP's, diltiazem, verapamil, and BB's or all on diltiazem.
   - Get blood levels

3. Thorough QT evaluation

   If any drug ever needed a "thorough QT evaluation," this is it, i.e., it needs an evaluation that probes the "worst case" blood level. On the other hand, if you feel that we really do understand the C/R for QT/QTc prolongation from available data (e.g., the concentration controlled I.V. study, CVT 3111, which pretty nicely showed effects of 4,000, 10,000, and 15,000 mg/ml, and showed good sized mean effects at the latter concentrations and near increases of 20+ msec at 4,000 mg/ml, with considerable variance) and know what various oral doses give in terms of concentration, maybe we know enough, although it remains unclear what to do with all that except worry.

4. Testicular problems

   Given the apparent absence of any other histopath problems than in the rat fertility study, isn't the most logical thing to do to just repeat it?

5. Interactions

6. I may have missed some of this, but it seems to me we need to understand all of the potential interactions and their interactions. If 200 mg ketoconazole gives a 3-4 fold increase in AUC/Cmax (which is it?) and verapamil and diltiazem give 2x increase, what do both do, especially in someone with a little liver problem? We really need to know this.

Robert J. Temple, M.D.

cc:
HFD-40/R Temple
draft:sb/10/28/03
final:sb/10/30/03
filename:Ranolazone_MM_Oct03.doc

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

/s/

Robert Temple
11/19/03 05:43:48 PM
MEDICAL OFFICER

Douglas C. Throckmorton, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Tel (301) 594-5365, FAX (301) 594-5494

Divisional Memorandum

DATE: 10.28.03

FROM: Douglas C. Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

SUBJECT: NDA 21-526
NAME OF DRUG: Ranolazine
SPONSOR: CV Therapeutics

DOCUMENTS USED FOR MEMO:

1. NDA submissions to 21-526, including letter to Robert Temple dated 10.20.03
2. Medical/Statistical Efficacy Review, by Shari Targum, M.D. and Valeria Friedlin, Ph.D., dated 8.28.03.
3. Medical Safety Review, by Maryann Gordon, M.D., dated 7.31.03.
4. Supervisory Medical Officer Review, by Norman Stockbridge, M.D., Ph.D., dated 9.29.03
5. Reports of bioequivalence study audits, by Nilufer M. Tampal, Ph.D., dated 8.5.03 and C.T. Viswanathan, Ph.D., dated 4.1.03.
6. Clinical study inspection report, by Robert Shibuya, dated 8.21.03.
7. Pharmacology/Toxicology Review by Elizabeth Hausner, Ph.D., dated 9.2.03.
8. Clinical Pharmaceutics and Biopharmaceutics review, by Nhi Nguyen, Ph.D., Atul Bhattaram, Ph.D., and Peter Hinderling, Ph.D., dated 8.18.03.
9. Chemistry Reviews, by N. Chidambaram, Ph.D., dated 9.16.03 and 10.10.03.
10. Carcinogenicity report to the Carcinogenicity Assessment Committee (CAC), by Elizabeth Hausner, Ph.D., dated1.31.02.
11. Executive CAC meeting summary, by Joseph Contrera, Ph.D. (for the Exec CAC), dated 1.29.02.
12. Memoranda on non-clinical electrophysiological and proarrhythmic effects of ranolazine, by John Koerner, Ph.D., dated 9.4.03, and 10.23.03.
13. Debarment Certification, dated 12.19.02.

CONCLUSIONS

This memorandum constitutes the Divisional memorandum recommendation that an approvable action be taken for the NDA named above for ranolazine in the treatment of angina. As summarized below, ranolazine SR, while efficacious as an antianginal in an undifferentiated population of patients, including patients receiving sub-maximal treatment with other antianginals, has sufficient safety concerns to warrant additional studies prior to approval. The safety concerns are two-fold:

1) Delayed cardiac repolarization, manifest by prolongation of the QT interval. For reasons discussed below, the available data are not reassuring as to ranolazine's arrhythmic potential.
2) Potential testicular toxicity, manifest as impaired fertility in rats. As discussed below, the data are inadequate to determine finally whether or not ranolazine has this effect. While no clinical signs of toxicity were reported, this is not surprising, and additional animal data are needed to characterize the effect of ranolazine on the testicle.

Regarding the consequences of the effects of ranolazine on cardiac repolarization, the most straightforward way to alleviate these concerns is to provide compelling data supporting novel therapeutic efficacy of ranolazine (*e.g.*, demonstrating efficacy in a resistant population). The sponsor has argued that they have identified such populations in post-hoc analyses of their database, and sufficiently demonstrated efficacy of ranolazine in that setting. As discussed below, neither the reviewers nor I am not at all convinced. Alternatively, the sponsor can argue that these issues do not represent safety concerns. Again, the attempts to convince the Division that the effects of ranolazine on QT are not concerning. The arguments, including those based on non-clinical work by Dr. Antzelovitch, are discussed extensively in the reviews (in particular, see Dr. Koerner's review). Overall, they are not compelling. In the end, for a drug like ranolazine, the available efficacy data are modest at best, and are simply insufficient to bear any significant safety concerns.

The drug has other issues to be resolved. They do not rise to the same level as the safety concerns identified above:

1) There is evidence suggesting a decreased/absent effect of ranolazine in women, an effect not related to differences in pharmacokinetics of the parent compound. This needs to be addressed in future studies or the drug should be clearly labeled to reflect this potential lack of efficacy (as the label will necessarily reflect the absence of data on non-White populations).
2) The dissolution testing for release needs to be adjusted per the recommendations of the Clinical Pharmacology team review.

BACKGROUND AND OVERVIEW

This submission includes over 200 clinical studies along with numerous non-clinical studies, stretching back to the early 70s. Much of the clinical data are of minimal use as regards efficacy of the current sustained-release formulation, and much of the animal work was done using a lower standard of quality than is now in place.

CHEMISTRY

The Chemistry Reviewer, Dr. Chidambaram, identified no deficiencies in the NDA submission for either the drug substance or product. Ranolazine has one chiral center, but is synthesized as a racemate (see his Review #1 for details). The drug product is an extended release product, achieved by placing the ranolazine in a pH-dependent polymer (dissolves at pH >5). The reviewer also identified no deficiencies in any of the associated Drug Master Files (page 7 of review #2). The categorical exclusion for the environmental assessment was submitted and found acceptable.

As regards shelf life, the reviewer recommends the addition of a retest date of [ ] for the drug substance and an expiration date of [ ] for the drug product, based on the stability data provided.

Good Lab Practices Site Reviews

The clinical and analytical portions of study CVT 301-15 (a bioequivalence study) were inspected. While a number of deficiencies were identified, none appear critical to the interpretation of the study.

PRE-CLINICAL PHARMACOLOGY TOXICOLOGY

The multitude of non-clinical studies have been reviewed primary by Elizabeth Hausner, Ph.D., along with some additional review of the 'QT' studies of ion channel activities by John Koerner, Ph.D.

Pharmacology: Receptor/Channel Effects

Ranolazine and its metabolites interact *in vitro* with a number of receptors and channels, including several relevant for cardiac function:

- Adrenergic receptors (especially alpha 1A, 1B and 2A)
- Serotonin receptor (5-HT1A)
- Calcium channels (both dihydropyridine and benzothiazepine types)
- Potassium channels and other channels affecting cardiac repolarization. John Koerner commented on the system used to assess this (in particular the HERG expressed in oocytes), and its deficiencies, such that the standard discussion of IC_{50} values is not relevant here (see his first memo, page 2). Suffice to say that inhibition of IKr was easily demonstrated at micromolar concentrations. Several of the metabolites also inhibit IKr, but the studies were done only at a single concentration. The effects of ranolazine on other relevant channels (*e.g.*, IKs, I_{Na}) have been the source of significant discussion by Dr. Koerner (his second memo deals with this issue

heavily). I take from his memos that the results are less clear than the sponsor asserts, and as a result less reassuring than they wish. As regards action potential duration, the sponsor looked at the effects of ranolazine in a number of repolarization and arrhythmia models (see Dr. Koerner's and Dr. Hausner's reviews for a discussion of their adequacy). Of particular interest, ranolazine prolongs the action potential duration in the M-cell region under conditions of hypokalemia. This is of some concern, as failure to prolong the APD in this region has been proposed as a putative marker for a drug that prolongs the QT 'safely'. The negative findings from the *in vivo* dog studies are of limited use for a variety of methodological reasons (see Dr. Koerner's first memo, pages 5-7).

- Miscellaneous other receptor binding: There is also evidence of binding to the opioid receptors (with 30% inhibitory concentrations of around 100 micromolar), although the significance of this binding is not known.

Pharmacology: Mechanism of Action

Simply put, any discussion of the mechanism of action is speculative, as was pointed out by several reviewers. First, as suggested from the receptor binding data above, ranolazine has a variety of effects on more standard vascular targets for an antianginal (*e.g.*, calcium channels) that could easily be linked to antianginal efficacy. There are other, more speculative, effects that the sponsor has chosen to emphasize when describing the effects of ranolazine. First, ranolazine does stimulate an increase in free fatty acid (FFA) and glucose uptake by the myocardium in disease models (*e.g.*, see CFT303.035-P in dogs with CHF, page 17 of Dr. Hausner's review). It also appears to decrease lactate efflux from ischemic myocardium and to protect against ischemia-reperfusion injury in a number of models, although no positive controls were included in the studies to provide a comparator for the relevance of the observed effects). Ranolazine inhibits fatty acid metabolism in several cardiac injury models (see pages 33-40 of Dr. Hausner's review for details).

Metabolism and Excretion

The metabolism of ranolazine is complex, and species-specific. The primary Clinical Pharmacology reviewer, Dr. Nguyen concluded that the primary route of elimination was via CYP 3A4, with a smaller fraction metabolized by CYP 2D6 (see her page 13). It is also a substrate/inhibitor of P-glycoprotein, explaining the interaction with digoxin and 'statins'.

The primary route of excretion for ranolazine is non-renal, with around 3% of an IV dose recovered unchanged in the urine and around 75% of radioactivity recovered in the feces.

Protein Binding

In a single study using human blood from 3 volunteers, 60-64% of radioactivity was bound to human plasma. Albumin binding was reported as 30% of the radioactivity. There is no evidence that the drug sequesters in RBCs (see Dr. Hausner's review, page 108).

General Toxicology

Many of the toxicology studies had a number of methodological flaws discussed by the reviewer, in part because they were conducted >10 years ago at a time when standardization of these studies was less.

Toxicities seen following short-term high doses included sedation, convulsions and ataxia. It is interesting that acute mortality (within minutes of drug administration) occurred in both rodent and non-rodent studies (for instance, see Dr. Hausner's review page 118). This mortality was associated with convulsions.

Toxicities following chronic administration included convulsions in the high-dose animals, vomiting, ataxia, subdued behavior and ophthalmic changes (pupils dilated, pupils non-responsive to light, conjunctival congestion), with no toxicities in the 3-month toxicity study at 5 mg/kg dose in dogs. Histopathological findings have not been presented in clear fashion by the sponsor, despite efforts by Dr. Hausner to obtain clarification, and apparently not collected from all animals, although the sponsor asserts there were no compound-related lesions seen in the high-dose animals.

In the one-year toxicology studies the findings included the ataxia and subdued behavior seen in the shorter studies (seen at ≥50 mg/kg dose for rats). There were slight decreases in hemoglobin and slight increases in reticulocytes counts and LDH, consistent with a hemolytic process seen in the high-dose groups (200 mg/kg/day in rats).

Special Toxicology (Cardiac, Adrenal)

Cardiac: Toxicology and ECG Interval Effects of Ranolazine

No effect on heart rate was seen in a 3-month study in dogs with doses up to 60 mg/kg/day (see Dr. Hausner's review page 128). Other ECG parameters are discussed above and by Dr. Koerner and Hausner in their reviews. No clear signal of concern regarding changes in the QT interval can be found in the standard cardiac evaluations of the animals, but methodological flaws prevent this from being reassuring. No arrhythmias were captured during the standard toxicology studies.

Cardiac: Channel Effects of Ranolazine

Dr. Koerner's reviews are thorough-going and critical with regard to the assertion by the sponsor that they have demonstrated that ranolazine is a 'safe' QT prolonger (see the letter to Dr. Temple dated 10.20.03). To summarize: the sponsor asserts that the effects of ranolazine on QT are 'fundamentally different from that of drugs known to cause torsade de pointes, and similar to that of drugs known to increase the QTc without causing torsades de pointes.' They believe the drug has different effects on the 'M-cells' of the myocardium, effects that predict a lack of arrhythmic potential. The M-cell data is derived from work done by Dr. Antzelevitch with his 'wedge-prep'. In this preparation, an increase in the transmural dispersion of repolarization is the critical parameter to be examined (dispersion is associated with an increased arrhythmic potential in the model). John has made a strong case, I believe, that even if we accept this argument (it has not been validated either prospectively or by looking at a large battery of compounds carefully) ranolazine still causes dispersion under conditions of hypokalemia. The sponsor has also made a case for effects of ranolazine at multiple channels, including some that would presumably decrease the arrhythmic potential (*e.g.*, late sodium current). John is also critical of this assertion, based on the way the studies in question were conducted, and the reader is referred to his memoranda for detail.

Other Organ-Specific Toxicities of Ranolazine

One organ-specific effect of note is an increase in adrenal weight and vacuolization. While small changes in serum sodium were reported sporadically in the toxicology studies, no evidence of metabolic effects of this increased weight was seen in the animal studies. A special study (see Dr. Hausner's review page 168) suggests an effect of ranolazine to reduce adrenal hormone production in animals; the clinical consequences of this are unknown.

A second 'organ-specific' effect of ranolazine comes from the observation that ranolazine binds to melanin, potentially leading to accumulation in the retina and in the skin. Again, the clinical consequences of this binding are unknown, although no gross ocular lesions were noted in the animal toxicity studies.

Genetic Toxicology, Carcinogenitiey, Reproductive Toxicity

As reviewed, ranolazine is neither mutagenic nor genotoxic. The *in vivo* mouse micronuclease assay did not meet the standards for testing today, and the reviewed concluded the results were 'equivocal', based on this failing.

With regard to carcinogenicity, the CAC reviewed the two carcinogenicity studies (rat and mouse) and concluded that 'there were no noteworthy findings'.

With regard to reproductive toxicology, Dr. Hausner has expressed concerns regarding the effects of ranolazine on male fertility from the rat studies (begins on page 187 of her review). Her concerns have also been addressed by Dr. DeFelice in his secondary review. The following is an attempt to summarize:

1) Male reproductive toxicity—there appears to be an effect of high doses to decrease male fertility, as measured by decreased percentage of successful matings in one study. In the rat fertility study, three males in the high-dose group were identified as having atrophic testes, thus contributing to the overall decreased fertility in that group. This may be related to a direct testicular effect or it may be a chance event that these males were all apparently in the high-dose group; here the data are not clear. As summarized by Dr. DeFelice, no evidence of histopathological effects was reported in the long-term rat and dog toxicity studies, but whether 'no change' was positively asserted, or simply nothing reported needs confirmed. Dr. Hausner has tried to clarify this without success with the sponsor. In his review, he believes a conservative estimate for the observed testicular toxicity seen in rats was at a dose that is 2X the clinical dose, not a reassuring multiple (but higher than the 0.03X multiple proposed by Dr. Hausner). In the end, I don't think we know enough about this to make a final conclusion. What is needed, as a start, is an evaluation of the long-term toxicity studies in rats and dogs.

2) Female reproductive toxicity—no evidence for that was seen by either reviewer.
3) Teratogenicity/ Developmental toxicity—Regarding teratogenicity, there was a nominal increase in the incidence of osseous malformations in rats exposed to ranolazine, but Dr. DeFelice did not view this as evidence for a teratogenic effect; rather, he felt it to be a commonly-observed finding in the population, irrespective of drug exposure. He otherwise saw no evidence for teratogenic effects in the data. Regarding development toxicities, there was some delay in development for rats exposed to ranolazine, although they 'caught up' by the end of the finals assessment. There was also a small decrease in rat newborn survival (around 100 to around 95% survival). Dr. DeFelice did not view the small decreases as a signal of concern. I do not see this as an approvability issue.

In the end, we don't have enough information to interpret the impaired fertility seen in the high-dose rats. In particular, absent histological data from the long-term toxicity studies, we don't know if the testicular effects were drug-induced or 'spontaneous'. A resolution of this deficiency will require, at a minimum, re-reading of the relevant tissue slices from the chronic tox studies conducted in rats and dogs. If this is not possible, additional studies are warranted. Should an animal toxicity be identified it will be important to characterize the clinical consequences of this animal toxicity.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The clinical pharmacology of ranolazine has been reviewed by a number of the Clinical Pharmacologists, including Dr. Peter Hinderling, Dr. B. Nhi Nguyen, Dr. Atul Bhattaram, and Dr. Joga Gobburu. Their combined review is a rich source of information; my summary should serve mainly to send the reader to that document. In addition, the modeling conducted by the group provides important additional information on the interactions of ranolazine with relevant demographics, drugs and disease states with regard to QT interval prolongation (begins on page 372 of the review). Some salient points from their reviews:

1) Ranolazine is well-absorbed, and there is no food effect.

2) The PK of ranolazine is not linear and not dose-proportional, but the increases in Cmax and AUC are not large (17 and 34% respectively). The terminal half-life is between 6 and 9 hours for the SR formulation.

3) While ranolazine is a racemate, the kinetics of the two forms are similar.

4) Ranolazine has a wide intersubject variability with regard to PK (CV 38-76%).

5) Ranolazine is metabolized via CYP 3A4 and 2D6, along with sulfatases and glucuronidases. The anticipated drug-drug interactions have been studied and confirmed (summarized on page 14 of the Clin Pharm review). It is a substrate/inhibitor of the P-glycoprotein transporter. It appears to be an inhibitor of 2D6, but at the concentrations likely to be achieved is not an inhibitor of 3A4 (see Clin Pharm review, page 102-3). The anticipated effects on QT interval related to concentration of ranolazine were seen for inhibitors of CYP 3A4; less is known for poor metabolizers related to 2D6.

6) The pharmacokinetics of ranolazine change with either hepatic or renal impairment, with increases in both Cmax and AUC in both populations increasing with increased severity of disease. The anticipated consequences of increased concentrations on QT were seen with renal impairment. There was an unanticipated (by me, anyway) interaction with liver impairment such that a given concentration caused a larger than anticipated prolongation of QT (see below).

7) There is a demonstrated relationship between ranolazine concentration and effect on exercise, and the Agency derived a PK-PD model for effect on exercise (not done by the sponsor). The Clinical Pharmacologists concluded the relationship was non-linear relationship, and the reviewers postulated that minor active metabolites might account for this observation. The non-linear nature of the relationship appears to have little consequence as to dosing. The model did not predict a plateau with regard to efficacy at higher concentrations. The reviewers also noted that gender was a significant cofactor in the model, reflecting the decreased effect of ranolazine in women (see Clinical section below). Their model also predicts an optimal 8-hour interdosing interval (see page 29 of the review for summary).

Biopharmaceutics

Bioequivalence of the to-be-marketed formulation and the clinical formulation were demonstrated. A biowaiver for lower strengths was approved given the dose-proportionality and comparable dissolution testing of the 375 and 500 mg SR strengths. The Divisions has recommendations about the appropriate dissolution testing to be done for release (see review page 7 of the Clin Pharm review); these should be transmitted to the sponsor.

Clinical Audits

Two sites were chosen for auditing because they were high enrollers in a pivotal trial. No issues were found on either inspection of substance, and the data, per Dr. Shibuya, 'appear acceptable.' No follow-up actions were recommended.

Efficacy

The reader is referred to the primary reviews for source material. Dr. Targum has correctly focused her attentions on the two trials conducted with the SR formulation of ranolazine (studies CVT 3031 and 3033). Both trials found a significant, if not overwhelming, effect on exercise tolerance testing (ETT) (see Dr. Targum's review, tables 5 and 6). Supportive analyses confirming the antianginal effect of ranolazine were effect seen on time to 1mm ST-segment depression (both studies), the use of nitrates (reduced with ranolazine in the one studied where it was measured, CVT 3033) and a reduction in the number of anginal episodes (from around 3.3 episodes to something around 2.2 episodes in study 3033). The trough effect was noticeably smaller than the peak effect (for instance, see table 6 from Dr. Targum's review). Some salient points from her review:

1) While antianginal efficacy was demonstrated adequately in two trials, the dose-response curve for efficacy is quite obscure, with little overall difference demonstrated for doses between 750 and 1500 BID. In study 3033, the doses of 750 and 1000 mg BID were not distinguishable from each other (her table, page 28). In study 3031, doses of 1000 and 1500 BID were not distinguishable from each other (her table, page 44).
2) As regards the interdosing interval, one trial clearly demonstrated antianginal efficacy at trough for the drug given BID. On this basis, the reviewer suggested the most appropriate dosing schedule remains to be determined. This was based primarily on her conclusion that there was a significant 'by period' interaction in the CVT 3031 trial, which was cross-over in design. When only the first period was examined, the trough results were no longer significant (see her discussion starting on page 44 of her review). The sponsor contests this, but the pharmacokinetics suggest that a more frequent dosing regimen could improve the overall efficacy. The clinical evidence is less clear-cut (Dr. Stockbridge concluded that a BID regimen was defensible, given the >50% retention of antianginal efficacy at trough, see his review, page 4).
3) There was evidence for persistence of antianginal efficacy, and no evidence for rebound angina through 12 weeks (see trial CVT 3033, which included a withdrawal period of 48 hours followed by an ETT). There is the suggestion in the one trial of significant length (3033) of reduced efficacy at weeks 6 and 12, compared with 2 weeks (her table 6, page 28).
4) Ranolazine has very small effects on blood pressure and heart rate (see table 17-18, and pages 37-38 in Dr. Targum's review).
5) Ranolazine appears to work on a background of other approved antianginals at less than maximal doses. Dr. Targum was not convinced that the sponsor had identified a population on maximally-tolerated or labeled doses of antianginals, or that they had demonstrated efficacy in such a population or populations (see her discussion beginning on page 16 of her review).
6) Like the Clinical Pharmacologists, she concluded that females benefited significantly less from ranolazine than men. This is seen vividly in the data from CVT 3033 (table 15).

Sub-Group Analyses of Efficacy

Dr. Targum and Stockbridge have written of the difficulties in sub-set analyses in this database, derived first and foremost from the marginal nature of the demonstration of efficacy; any splitting of the overall population will leave you with small sub-groups and uncertain power to see anything by noise. For some subsets (non-White) there are simply too few individuals to even try to look (a thing not to be lost in any future labeling). For other subsets, women and patients with CHF, there is some evidence for reduced efficacy that bears a bit more examination. Dr. Targum has summarized the primary findings from the 3033 study by gender and presence of CHF on page 31 of her review (table 11). The decrease in change in exercise tolerance is especially striking for women, and to a lesser degree for CHF. The Clinical Pharmacology reviewer, Dr. Hinderling, agreed that there was evidence of decreased efficacy in women, an effect not attributed to differences in kinetics (see his comments, page 38 of the Clin Pharm review). The sponsor should be asked to describe this effect more fully, or be prepared to label the drug as less efficacious (for a given dose/concentration) in women. The population with CHF seems less clear, and I would remain silent on it given the uncertainty of subset analyses.

Safety

Overall Safety

Dr. Gordon has reviewed the overall safety database, and no alarming signals for rare (*e.g.*, liver injury) or unanticipated adverse effects of ranolazine emerge. A number of constitutional adverse events seem demonstrably higher in the ranolazine group (*e.g.*, see her table on page 17 from the controlled angina trials—dizziness, constipation, nausea, asthenia). The majority of these are monitor able (which provides some reassurance) and they also appear dose-related (which might limit dose-exposure in some patients—reassuring?). The overall size of the safety database is small for angina, although the data from the immediate release experience helps some for lower doses than would be used here. It's worth noting that only one of the angina trials exposed subjects to a given dose of drug for more than a week.

Effects on QT/QTc

The clinical effects of ranolazine on the QT have summarized by several other reviewers, most concisely by Dr. Stockbridge. Dr. Bhattaram has also performed elegant modeling of the available data (begins on page 375 of the Clinical Pharmacology review). Some salient points to make:

1) That ranolazine prolongs the QT interval is accepted by all parties. At 1500 mg BID (less than 2X upper dose proposed by the sponsor of 1000 BID), the prolongation is around 12 msec in the overall population. At this dose, 7.5% of the individuals had QT >500 msec[1]. Keeping the dose below 1000 mg BID would limit the QTc prolongation to somewhat less than 10 msec, but large inter-subject variability in pharmacokinetics and drug metabolism will still have individual with larger effects (suggested by the percentage of outliers).

2) That ranolazine has a more dramatic effect on the QT interval in patients with hepatic impairment is accepted by all parties (see table below). Of interest, the modeling conducted by the sponsor suggests the relationship between concentration and effect on QT is non-linear(Clin Pharm review, page 405), although no rationale for this difference from the findings in patients without hepatic impairment is forwarded (although Dr. Stockbridge questions whether a non-linear relationship might not be appropriate for all populations).

QTc Prolongation Following Ranolazine[2]

	Change in QT
Population excluding hepatic impaired	2.56 msec per 1000 ng/ml ranolazine[1]
Hepatic impairment population	7.10 msec per 1000 ng/ml ranolazine[1]

1. Serum concentration. For reference, the typical doses of ranolazine achieve concentrations <10,000 ng/ml.
2. From Clin Pharm review, page 382.

This observed difference in the concentration-effect relationship for QT prolongation is as dramatic as any I am aware of (we have little data in this regard, however).

3) Inhibitors of CYP3A4 increase blood levels by around 2-fold, with their associated expected effect on QTc interval.

4) Other ECG markers of uncertain concern include an increase in the frequency of 'notched' T-waves. At very high levels of ranolazine (10,000 ng/ml) their frequency was 75% (see Dr. Gordon's review, page 37).

5) Clinical signs of arrhythmias have apparently not been systematically summarized in other reviews.

a) Deaths: in a total exposure of 2682 patients there were 29 deaths on ranolazine through 10.15.01, of which 13 were described by the reviewer as 'sudden' (no definition available to me, Dr. Gordon's table page 18). This fraction (45%), with all its uncertainties, is somewhat higher than other drugs that have been approved and do not appear to cause torsade de pointes (TdP) (range 0-20%, n=3) and in the range for surveyed drugs that cause TdP (30-55%, n=4). However, of the four deaths in patients exposed to placebo (all short duration exposure), two were defined as 'sudden'. I believe we have too few deaths to draw any meaningful reassurance and too little information about most of them to draw any meaningful concerns from such analyses.

b) Clinical Adverse Events: there were no cases of TdP reported by the sponsor. Discontinuations due to dizziness occurred more frequently in patients taking ranolazine (1.0% vs. 0.1% in placebo, see Dr. Gordon's table 25R). Palpitations and dizziness were also reported as adverse events more frequently in the ranolazine group in the integrated safety population (2.4% vs 1.0% and 13.2% vs. 2.9%

[1] See Dr. Gordon's review, page 55, table 39R. The sponsor disputes this figure based on the selection of a single lead rather than any lead.

respectively, Dr. Gordon's page 16, table 12). Syncope was reported only in patients on the two highest doses of ranolazine (see her table page 18).

In the end, this is not a reassuring database. Despite the small numbers, the clinical events clearly raise some concern, especially for a drug that does not decrease heart rate or blood pressure appreciably (removing other, usual reasons for these events). While there could be other reasons for each and every one of these clinical observations, these findings, coupled with the presence of sub-populations like the hepatically-impaired where ranolazine has much larger effects on the QT, leads me to conclude that this is a safety concern that needs to be addressed with a larger safety database (size undetermined) or offset by substantive evidence of meaningful efficacy (discussed below).

SUMMARY

That ranolazine is effective as an antianginal in an undifferentiated population with angina is not an issue, although the efficacy data for trough dosing using a BID regimen are not overwhelming and it is unclear precisely what doses of ranolazine to recommend for use (certainly no rationale for recommending anything above 1000 mg BID, maybe even 750 mg BID). The efficacy data also rest on a single trial lasting more than one week of exposure, a small database, particularly given the uncertainty about how to dose ranolazine and the suggestion of reduced efficacy in women. Study 3033 did look at a variety of parameters linked to antianginal efficacy, and all tell a similar story of modest efficacy in the population studied. These effects on the symptoms of angina are, however, insufficient to offset the identified safety concerns (which include potential testicular toxicity and demonstrated QT prolongation). The available data, both non-clinical and clinical, do not provide comfort as to the proarrhythmic risk of this compound. On the contrary, given the absence of significant hemodynamic effects, the observed increases in the incidence of dizziness and palpitations give one pause, even if these adverse events are typically very difficult to interpret.

Given the symptomatic nature of the efficacy claim, and the availability of other antianginals that lack these issues, additional data are needed to offset or alleviate the identified safety concerns. As for the potential testicular toxicity, additional evaluation of currently available data may well suffice to resolve the issue. As for the QT effects, the most direct way forward would be to demonstrate a benefit for ranolazine not shared by other agents (*e.g.*, efficacy in prospectively-define resistant populations, benefits on more durable clinical endpoints). The collection of such data would provide an additional trial to collect more information on the dosing of ranolazine, and additional safety exposure as well. Given the availability of other therapies, there is no attraction to considering these studies as Phase IV commitments.

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/s/

Doug Throckmorton
10/30/03 07:26:52 AM
MEDICAL OFFICER

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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Transmitted to FAX Number:	(650) 494 - 8769
Attention:	**Ms. Carol Karp**
Company Name:	CV Therapeutics
Phone:	(650) 384 - 8875
Subject:	Minutes from the October 29, 2003 telecon
Date:	11/21/03
Pages including this sheet:	6

From: **Meg Pease-Fye**
Phone: **301-594-5312**
Fax: **301-594-5494**

You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

PLEASE LET ME KNOW YOU RECEIVED THIS. THANK YOU!

Minutes of a Meeting

Date of meeting:	October 29, 2003
Product:	Ranexa (ranolazine) 375 and 500mg extended release Tablets
Application:	NDA 21-526
Sponsor:	CV Therapeutics
Purpose:	Pre-decisional meeting

Attendees

Division of Cardio-Renal Drug Products

Robert Temple, M.D., Director, Office of Drug Evaluation I
Douglas C. Throckmorton, M.D., Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D., Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D., Medical Team Leader, HFD-110
Shari Targum, M.D., Medical Officer, HFD-110
Mehul Desai, M.D., Medical Officer, HFD-110
Salma Lemtouni, M.D., M.P.H., Medical Officer, HFD-110
Valeria Freidlin, Ph.D., Biometrics, HFD-710
James Hung, Ph.D., Team Leader, Biometrics, HFD-710
Elizabeth Hausner, D.V.M., Pharmacology, HFD-110
John Koerner, Ph.D., Pharmacology, HFD-110
Albert DeFelice, Ph.D., Team Leader, Pharmacology, HFD-110
Atul Bhattaram, Ph.D., Clinical Pharmacology and Biopharmaceutics, HFD-860
Nallaperumal Chidambaram, Ph.D., Chemistry, HFD-810
Kasturi Srinivasachar, Ph.D., Team Leader, Chemistry, HFD-810
Edward Fromm, Regulatory Health Project Manager, HFD-110
Meg Pease-Fye, Regulatory Health Project Manager, HFD-110

CV Therapeutics

Brent Blackburn, Ph.D., Senior Vice President, Drug Discovery and Pre-Clinical Development
Carol Karp, Vice President, Regulatory Affairs
Louis Lange, M.D., Ph.D., Chairman, Chief Executive Officer
Michael Sweeney, M.D., Vice President, Medical Affairs
Andrew Wolff, M.D., F.A.C.C., Senior Vice President, Clinical Research and Development

Consultants

Peter Kowey, M.D., F.A.C.C.
[redacted]
Jeremy Ruskin, M.D.

Background

Ranolazine SR is being developed for treatment of chronic angina in patients with severe coronary artery disease in whom other anti-anginals are inadequate or not tolerated. A Discipline Review letter was sent to the Sponsor on July 17, 2003 identifying specific concerns with the application. A submission received by the Division on September 15, 2003 did not constitute a major amendment and the PDUFA goal date for the application remained October 30, 2003. An October 1, 2003 teleconference was held during which it was agreed that ranolazine would go before the December Cardio-Renal Advisory

Committee. The applicant requested this meeting to clarify the Agency's concerns prior to the October 30, 2003 goal date.

Meeting

Dr. Temple began by summarizing some of his concerns with the safety and efficacy of this application. He stated that

- The safety database is very modest for this indication. Much of the immediate-release data is irrelevant to safety as it was from patients who received doses that were lower than currant proposed doses; only 600 – 700 of patient, well below the ICH 1500 patient expectation seem to have received doses proposed by the Applicant.
- How to dose this drug with its variable bioavailability is unclear, despite a good definition of the concentration-effect relationship. The crossover study provides a suggestion of dose-response, but in that study, ranolazine was not used with other drugs, like diltiazem and verapamil, which cause higher blood levels of the drug.
- Other than one 12-week study (CARISA), most of the data is from short-duration (one week) or single-dose studies, for less support than we have seen with anti-anginal drugs.

He concluded that the Agency wants to see more data, specifically more dose-response data, and data from patients already on maximal doses or maximally tolerated doses of either beta-blockers or calcium channel blockers.

CV Therapeutics noted a 25% decrease in angina episodes versus placebo in the CARISA study and believe that ranolazine could have a significant impact on the reported anginal attacks each year. They also believe that their drug acts by a different mechanism from other anti-anginal therapies, as there is little effect on blood pressure or heart rate. They also noted that small increases in heart rate were observed with higher doses of the drug, but they believe efficacy is independent of these effects. Dr. Temple responded that there is still significant angina present even after patients receive the drug and that whether there is a novel (non-heart rate or pressure-related) effect is not clear. CV Therapeutics acknowledged that in effectiveness trials of the controlled release product, there was no increase in rate-pressure products at maximal exercise. This suggests no effect on maximal oxygen utilization and raises doubt about the presence of a different mechanism of action

Dr. Temple questioned how ranolazine should be used, asking about titration plans that would lead to effectiveness but not toxicity, especially QT prolongation. CV Therapeutics responded that the intent was to start at a low dose, as typically, adverse events at lower doses were comparable to placebo and there seemed little QT effect. Dr. Temple replied that the dose-response is still unknown, although the concentration-response appears acceptable, it was not clear how to utilize that information.

CV Therapeutics acknowledged that the Agency had previously requested a study in a refractory population. Although there is some data in such patients, they understand the Agency does not think it is enough. They noted concern about the Advisory Committee panel potentially being biased from the Agency's action letters. Dr. Throckmorton explained that the language in action letters specifically describes the weak areas of the application and suggests possible avenues for addressing these weaknesses. CV Therapeutics will have a clear opportunity to explain why they disagree.

CV Therapeutics asked about the timing of the action, noting that it usually occurs after the Advisory Committee meeting. Dr. Throckmorton replied that the Advisory Committee will address the issues raised and does not need to agree with our conclusions. The committee exists to give independent advice.

Dr. Temple added that the committee will know that the Agency is taking an action because the Division has reached these conclusions:

- ranolazine has an effect in angina, but the safety database is small and there is only one effectiveness study of greater than one week duration.
- ranolazine prolongs QT interval, and we do not see reasons to believe this will not give a risk of Toursades de Points if the effect is large enough.
- ranolazine's effect may decline over time; it did in the 12 week study, the only study of more than one week duration.
- pre-clinical observation shows testicular toxicity.

Dr. Temple also noted that ranolazine blood levels are increased if it is administered with other drugs such as diltiazem or verapamil and that pushing the dose to gain a greater effect might be seen in a post-market setting. CV Therapeutics believes that physicians would not titrate because the higher doses are poorly tolerated and further suspect that the doctors would be inclined to add other available therapies, such as beta-blockers or calcium channel blockers (CCBs), rather than pushing the dose.

CV Therapeutics asked if a study was performed in refractory patients, should the patients be on all or some of the usual anti-anginal therapies (β-blockers, CCBs) and ranolazine? The Agency replied that ranolazine should be used on top of maximally tolerated doses of one other available therapy (β-blockers, or CCBs).

Dr. Temple encouraged a study coupling dose to concentration. Dr. Throckmorton noted he wants to see what effects are seen when 500 mg is given versus when 1500 mg is given and this type of study needs to be a randomized study. The applicant acknowledged that they need to find a refractory population and asked whether there are no revascularization or other medical options for patients with angina, would it be feasible to pursue a Subpart H approval in these patients? Dr. Temple responded that angina symptoms are not a serious or life-threatening disease, and that treadmill time is already a suitable endpoint, just one that has not yet been adequately studied for ranolazine. Further, he noted that it appears that ranolazine causes only a modest decrease in symptoms and he asked how much risk is that worth, an issue the Advisory Committee would consider.

Conclusions
An action will take place on October 30, 2003. A teleconference will take place on Monday, November3, 2003 to discuss strategies for the Advisory Committee meeting on December 9, 2003.

Signature minutes preparer: _____
Meg Pease-Fye

Concurrence, Chair: _____
Robert Temple, M.D.

Drafted 10.30.03 Finaled 11.21.03
RD:
R Temple 11.19.03
D Throckmorton 11.19.03

N Stockbridge	11.06.03
T Marciniak	11.06.02
S Targum	11.06.03
V Freidlin	11.05.03
J Hung	11.05.03
E Hausner	11.05.03
J Koerner	11.05.03
A DeFelice	11.05.03
A Bhattaram	11.06.03
N Chidambaram	11.04.03
K Srinivasachar	11.04.03
E Fromm	10.30.03

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/s/

Robert Temple
11/21/03 12:12:20 PM

CV Therapeutics

October 20, 2003

Robert Temple, M.D.
Acting Director
Office of Drug Evaluation
HFD-040
1451 Rockville Pike, Room 6014
Rockville, MD 20852

Dear Dr. Temple:

We appreciate the opportunity to meet with you and Drs. Throckmorton and Stockbridge at 9:00 a.m., October 29, 2003. At this meeting, we would like to discuss our risk management proposals, including a large simple study (similar to the ZODIAC study with ziprasidone), to support a first-cycle approval of Ranexa™ (ranolazine) for chronic angina by the PDUFA-mandated action date of October 30, 2003.

Ranolazine is effective in treating chronic angina. The anti-anginal and anti-ischemic benefits of ranolazine have been demonstrated across a broadly representative population of chronic angina patients in two pivotal and three supportive trials. The efficacy of ranolazine has been demonstrated both as anti-anginal monotherapy and when given over a background of beta-blockers or calcium channel blockers, including atenolol or diltiazem, each under conditions of their maximal effect. Furthermore, these anti-anginal and anti-ischemic effects of ranolazine do not depend upon reductions in blood pressure or heart rate, a pharmacodynamic profile unavailable among the currently approved anti-anginal drugs.

Accompanying the demonstrated anti-anginal and anti-ischemic benefits of ranolazine is a well-characterized effect to prolong the QTc interval, which is of uncertain clinical significance. Ranolazine increases QTc by about 2 - 5 msec, on average, over the currently recommended dose range at peak. Even with maximum inhibition of its major elimination pathway by ketoconazole, QTc increases on ranolazine are about 10 - 20 msec, over the recommended dose range at peak. A secondary elimination pathway (via cytochrome $P_{450}2D6$) and intolerable side effects at supra-therapeutic plasma concentrations further limit the risk of exposure to plasma ranolazine concentrations which might be associated with QTc increases > 20 msec.

Furthermore, extensive pre-clinical data demonstrate that the cellular electrophysiological profile underlying the QTc effect of ranolazine is fundamentally different from that of drugs known to cause torsades de pointes, and similar to that of drugs known to increase the QTc without causing torsades de pointes.

In pre-clinical models, ranolazine does not provoke early afterdepolarizations or increase the dispersion of repolarization, phenomena which appear to be better markers of pro-arrhythmia than clinical QTc measurements. Use of these pre-clinical screens would have successfully predicted the arrhythmogenic potential of such drugs as terfenadine, mibefradil, and cisapride. In fact, ranolazine prevents the development of -- and even actively reverses -- these pro-arrhythmic signals when drugs known to cause torsades have induced them.

Consistent with these observations, during 1714 subject/patient years of exposure in 2783 individuals with a mean treatment duration of 225 days, there has been no clinically evident safety concern with ranolazine. Treadmill exercise criteria for randomization into the two pivotal studies, MARISA and CARISA, ensured a Duke Treadmill Exercise Score of minus 10 or lower in these patients. The 2002 ACC/AHA Practice Guidelines for chronic angina management[1] cite a 5% annual mortality in such patients; however, first-year mortality in our population remains at 2%, and there has never been a documented case of torsades de pointes on ranolazine.

The pharmacodynamic profile of ranolazine addresses an unmet need for a non-hemodynamic anti-anginal agent. In patients whose angina cannot be eliminated by combinations of beta-blockers, calcium channel blockers and nitrates, it is often these drugs' depressive effects on blood pressure, heart rate, contractile function and/or AV nodal conduction, as well as other dose-related side effects, which limit further dose escalation and preclude complete relief from angina. Myocardial revascularization cannot be accomplished in many of these patients, leaving them with no therapeutic alternative. These patients – who stand to benefit most from ranolazine – are readily identified, and their response to ranolazine treatment can be assessed during a relatively brief exposure to the drug.

Physicians can determine which patients benefit from ranolazine with a reduction in angina symptoms; therefore, the goal is to minimize any risk associated with the QTc effect. Accordingly, CVT has developed a comprehensive risk management program for ranolazine that is detailed below. Such a risk management program requires two components. The first is further research and monitoring to expand the knowledge of the risk (if any). The second component is an active communication initiative, which ensures that this knowledge is known to health care professionals and is regularly updated.

---

[1] Gibbons et al., 2002; available at www.acc.org/clinical/guidelines/stable/stable.pdf

Knowledge Expansion

CVT is committed to ongoing research to gain additional knowledge of the benefits and risks of ranolazine following its approval by the Agency. A variety of methods will be employed to expand this knowledge based on sound scientific and epidemiological principles.

The following methods of further evaluating the risk (if any) are available:

1. Large simple trials (LSTs)
2. Controlled clinical trials
3. Cohort and database studies
4. Monitoring and evaluation of spontaneous post-marketing adverse events

Subject to further discussion and agreement with the Agency, CVT proposes scientifically-based risk management initiatives in each of these areas to assure the safe use of ranolazine following its approval,

1. A Large Simple Trial (LST)

   LSTs are emerging as the preferred way to quantify the clinical significance of any QTc effect in real clinical practice. In order to be relevant to real-world clinical practice in the intended population, and to enroll sufficient patients, LSTs must be done post-approval. A current ongoing LST is the ZODIAC study for ziprasidone, an anti-psychotic medication with a QTc prolongation effect similar to that of ranolazine.

   CVT proposes a post-approval LST of ranolazine in approximately 8000 chronic angina patients who are receiving a beta-blocker, who require additional anti-anginal therapy, and who would be appropriate candidates for either amlodipine or ranolazine. Randomization would be 1:1 between amlodipine and ranolazine. The final study design will be clarified in discussion with appropriate experts and agreed with the Agency. Assuming 4% annual mortality, 8000 patients provide 80% power to exclude a relative risk of 1.3 with a two-tailed alpha error of 5%.

2. A Controlled Clinical Trial: Study CVT 3036

   CVT has already submitted this protocol for review by the Agency and has requested a meeting to discuss it. This prospective, randomized, double-blind, placebo-controlled study will be sponsored by CVT and run by the TIMI Research Group, Boston, MA, under the direction of Dr. Eugene Braunwald. The trial will enroll up to 5500 patients admitted to hospital with non-ST segment elevation acute coronary syndromes who are at increased risk for subsequent cardiovascular events.

Acute treatment with intravenous ranolazine (or placebo) in addition to standard therapy (including optimal revascularization when possible) will be followed by long-term therapy on oral ranolazine (or placebo). The primary endpoint is proposed to be a composite of the first occurrence of cardiovascular death, myocardial infarction, or recurrent ischemia.

The mean duration of follow-up in the 5500 coronary artery disease patients to be enrolled in Study CVT 3036 is estimated to be about one year, which should provide a useful assessment of the clinical significance of QTc prolongation on ranolazine. A Data Safety Monitoring Board will review data from the study as it progresses. The controlled data from this trial will be a major component in the quantification of the benefits and risk (if any) of ranolazine in a large varied population similar to that anticipated to be prescribed the drug for the treatment of chronic angina in general cardiologic practice.

3. Cohort and Database Studies

CVT currently sponsors a large observation cohort study, PREMIER-QI (Prospective Registry Evaluating outcomes after Myocardial Events: Quality Improvement), investigating angina incidence and outcomes following an acute cardiac event. The PREMIER-QI study is an alliance of leading cardiac centers coordinated by the Cardiovascular Outcomes Research Consortium (CORC) and includes such institutions as Stanford, Yale, Duke, and Emory Universities. PREMIER-QI has enrolled 2,500 patients presenting with an acute myocardial infarction, who are then followed after discharge to determine their subsequent course. There is particular focus on recurrent cardiovascular events; on the frequency, severity, and impact of angina; and on the overall impact of cardiovascular disease on their lives and healthcare resource utilization. This cohort, although not treated with ranolazine, will be used in the risk management program to supply information on expected background events and outcomes in a high-risk population.

In addition to this background study, the feasibility of a prospective follow up of a ranolazine-treated cohort will be explored using an existing Medicaid or Managed Care Organization (MCO) database with the potential to track prescribing. Prescriptions for Ranexa will be crosschecked with these databases to ensure that there is minimal co-prescription of concomitant medications that are advised against in the approved product label. This method of study both documents the success of communication efforts and also targets areas for more focused communication early post launch.

4. Monitoring and Evaluation of Spontaneous Post-Marketing Adverse Events

CVT will employ an aggressive monitoring and follow-up procedure for all spontaneous adverse events reported to the company following approval of Ranexa.

Beyond this standard process, the following additional measures will also be implemented following discussion with Agency.

For a number of selected adverse events, detailed questionnaires will be developed for use when these events are reported to CVT. This will ensure that as far as possible, all relevant information can be obtained to allow detailed evaluation of both the adverse event and any patterns. The events selected for detailed assessment will be discussed with the Agency. The agreed events will be reported to the Agency on an expedited basis to allow as far as is possible real time evaluation by both CVT and the Agency. Prescribers will be made aware of a 1-800 number to report adverse events to the company on a timely basis.

Summaries and evaluations for each of the agreed adverse events will be reported to the Agency on a quarterly basis for the first three years following approval or until a mutually agreed time. In this way any signals, should they occur, will be flagged to the Agency at an early stage to allow for a rapid agreement as to further management and investigation of potential relationship to drug therapy.

The comprehensive knowledge expansion program proposed above explores a series of data sources and study methods. It is important, however, that this program is complemented by an aggressive communication program at launch and on an ongoing basis to ensure that the information generated reaches and is acted upon by the prescriber.

Communication Initiative

The label will be the primary resource for communicating safety information for Ranexa to prescribing healthcare practitioners, supplemented by additional targeted initiatives to enhance safe use of the medication. These initiatives will emphasize appropriate patient selection, vigilance for and prevention of use of concomitant interacting medications, and the monitoring and management of potential adverse events if they occur. Appropriate communication efforts are targeted toward physicians, pharmacists, and patients.

Consideration of 750 mg bid as the Maximum Dose at Launch

The current proposed labeling gives a dose range of 500 mg bid to 1000 mg bid for most patients. A dose range of 375 to 750 mg b.i.d. is given for patients with severe renal impairment (CLcr <30 mL/min), and for patients treated with diltiazem ≥240 mg/day or verapamil ≥360 mg/day. As noted earlier in this letter, over this recommended dose range, QTc increases by about 2 – 5 msec, on average, at peak. With ketoconazole, QTc increases on ranolazine are about 10 – 20 msec over this recommended dose range at peak. Because these QTc increases are linear with dose and plasma concentration, reduction of the maximum dose to 750 mg would proportionally limit the QTc increase with ketoconazole to about 7.5 – 15 msec. Furthermore, in the pivotal studies, adverse events in general were less frequent on 500 mg bid and 750 mg bid than on 1000 mg bid.

Accordingly, CVT is willing to discuss the exclusion of the 1000 mg dose from the label at the time of the initial launch.

In summary, CVT has demonstrated the anti-anginal and anti-ischemic benefits of ranolazine in chronic angina, which can be confirmed in individual patients through clinical observation by their physicians. The QTc effects have been well characterized clinically and have been shown to derive from a unique cellular electrophysiological profile that is fundamentally different from that of drugs known to cause torsades de pointes. With the risk management initiatives proposed above, CVT can ensure the safe use of ranolazine in those patients who benefit from it.

Yours truly,

Louis G. Lange, M.D., Ph.D.
Chairman and CEO

Andrew Wolff, M.D., F.A.C.C.
Sr. Vice President
Clinical Research and Development

LGL/AAW/jmm
.102003Dr.Temple

********** -COMM. JOURNAL- ********** DATE OCT-06-2003 ***** TIME 13:15 *********

MODE = MEMORY TRANSMISSION START=OCT-06 13:14 END=OCT-06 13:15

FILE NO.=278

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
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-FDA,CDER,OND,ODEI,DCRDP -

********** -CARDIO RENAL - ***** - 301 594 5494- **********

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Transmitted to FAX Number:	(650) 494 - 8769
Attention:	**Ms. Carol Karp**
Company Name:	CV Therapeutics
Phone:	(650) 384 - 8875
Subject:	Minutes from the October 1, 2003 telecon
Date:	10/6/03
Pages including this sheet:	3

From: **Meg Pease-Fye**
Phone: **301-594-5312**
Fax: **301-594-5494**

You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

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Minutes of a Teleconference

Date of teleconference:	October 1, 2003
Product:	Ranexa (ranolazine) 375 and 500mg Extended Release Tablets
Application:	NDA 21-526
Sponsor:	CV Therapeutics
Purpose:	To discuss whether the last submission (dated September 13, 2003) is a major amendment

Attendees

Division of Cardio-Renal Drug Products

Douglas C. Throckmorton	Director, Division of Cardio-Renal Drug Products, HFD-110
Zelda McDonald	Chief, Project Management Staff, HFD-110
Meg Pease-Fye	Regulatory Health Project Manager, HFD-110

CV Therapeutics
Brent Blackburn, Ph.D., Senior Vice President, Drug Discovery and Pre-clinical Research
Margaret Dillon, Ph.D., Senior Director, Regulatory Affairs
Carol Karp, Vice President, Regulatory Affairs
Louis Lange, M.D., Ph.D., Chairman and Chief Executive Officer
Sandy Skettino, M.D., Senior Vice President, Clinical Research and Development
Andrew Wolff, M.D., Senior Vice President, Clinical Research and Development

Background
Ranolazine SR is being developed for treatment of chronic angina. The Agency requested this teleconference to discuss whether or not the submission received by the Division on September 15, 2003 constitutes a major amendment. The PDUFA goal date for the application is October 30, 2003. The applicant is proposing that the submission would allow for an extension of the PDUFA goal date by 90 days.

Telecon
Dr. Throckmorton began by making two key points:

- The submission received on September 15, 2003 does not constitute a major amendment and Dr. Temple intends to meet the PDUFA goal of October 30, 2003.
- The Agency is willing to plan to discuss the product, at an Advisory Committee meeting on December 9, 2003.

The applicant expressed willingness to go to the Advisory Committee, and then asked what issues would likely be discussed. Dr. Throckmorton responded that they were the same issues the reviewers have been addressing, pertaining to the drug's safetyand the necessary efficacy data to support its use. CV Therapeutics stated that they wanted to find a way to avoid an action letter that might potentially bias the Committee. They asked about a face-to-face meeting with Drs. Temple and Throckmorton prior to the action. The available data were discussed, and Dr. Throckmorton reiterated that he could not speak for

Dr. Temple or what his decision might be, but that the Division had sufficient information to make a recommendation to him. Dr. Throckmorton stated that the sponsor would need to request a face-to-face meeting through Dr. Temple's office if desired, and he couldn't say if such a meeting could be arranged.

Action item
Ms. Pease-Fye will set up a teleconference with the Sponsor for early November to discuss the Advisory Committee meeting.

Signature minutes preparer: Meg Pease-Fye 10.6.03
Meg Pease-Fye

Concurrence, Chair: [signature] 10.6.03
Douglas C. Throckmorton, M.D.

Drafted 10.03.03 Finaled
RD:

EFromm for ZMcDonald-10.6.03
Throckmorton 10.6.03

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Transmitted to FAX Number:	(650) 494 - 8769
Attention:	**Ms. Carol Karp**
Company Name:	CV Therapeutics
Phone:	(650) 384 - 8875
Subject:	Minutes from the September 3, 2003 telecon with Biostatistics
Date:	9/10/03
Pages including this sheet:	3

From:	**Meg Pease-Fye**
Phone:	**301-594-5312**
Fax:	**301-594-5494**

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Minutes of a Teleconference

Date of teleconference: September 3, 2003

Product: Ranexa (ranolazine) 375 and 500mg extended release Tablets
Application: NDA 21-526
Sponsor: CV Therapeutics

Purpose: To further discuss reviewer comments

Attendees

Division of Cardio-Renal Drug Products
Valeria Freidlin, Ph.D., Statistics, HFD-710
James Hung, Ph.D., Team Leader, Statisitics, HFD-710
Meg Pease-Fye, Regulatory Health Project Manager, HFD-110

CV Therapeutics
Michael Crager, Ph.D., Senior Director, Biostatistics
Margaret Dillon, Ph.D., Senior Director, Regulatory Affairs
Carol Karp, Vice President, Regulatory Affairs
Whedy Wang, M.P.H., Ph.D., Executive Director, Biometrics
[redacted] Consultant, Statistician

Background
A discipline review letter was sent to the sponsor on July 16, 2003 and a teleconference was held on July 18, 2003 both to give the Sponsor an indication of the Agency reviewer's concerns about the pending application. This telecon is one in a series to go over these issues in efforts to resolve them. This telecon is a follow-up to the August 11, 2003 telecon and will discuss information presented by the Sponsor in a submission of August 18, 2003.

Meeting
The Sponsor verified that the issue of carry-over effect was no longer a concern to the Agency, and that the period-by-treatment interaction warranted further analysis, leading to the August 18, 2003 submission. Dr. Hung acknowledged that he had read their analysis and believed that the results were similar to those from the previous submissions. He is still concerned about the patterns in table ET-13A (from June 17, 2003 submission), recognizing that the variability is large. The Sponsor replied that in table 2, they provided period comparisons with the treatment comparisons and showed there were no obvious dose-related trends in the slope. Dr. Hung said the trend in table ET-13A shows that the ranolazine doses show numerically larger slopes (except possibly the 1000mg dose, but for this dose, the 4thperiod data appeared to be influenced by placebo in the immediately preceding period) was still troubling, though the trend was inconclusive. The Sponsor argued that the patterns were consistent with sampling variability. Further, they believe the more precise General Linear Models (GLM) analysis reinforced the results given by the earlier General Estimating Equations (GEE) analysis, which showed that the treatment by period interactions were eliminated. They also remarked that they used one standard error instead of two in figure 3, and that the patterns were random. Dr. Hung replied that he still sees a consistent pattern that concerns him.

The Sponsor continued saying that patients in the CARISA trial were on background therapy, and that the cross-over study was monotherapy. They believe that looking at treatment effects over time, there is an effect at each week interval and it is constant over time. Dr. Hung remarked that he saw the ranolazine effect seemed to decrease over time (in weeks) in Study 3033. The Sponsor disagreed, and they see a different trend.

The Sponsor asked what they can do to resolve this issue of the crossover study. Dr. Hung said that he could not think of any additional analysis for them to perform.

Dr. Freidlin noted a poor fit in figure 3 for the placebo and the highest dose. She sees a period -by-treatment interaction in the data. The Sponsor disagreed, that there is no interaction because the data includes 0 in the confidence interval. They argued that a perfect math model is impossible when there is so much random variability. Dr. Freidlin responded that the residuals do not look random, and that there is a pattern in the placebo and highest dose groups. Further, in terms of duration of exercise, she stated that the carry-over might take the form of a learning effect. Dr. Freidlin reminded the Sponsor that in an April 30, 2003 submission, the Sponsor stated that there is a strong period effect which represents a training or learning effect in the exercise treadmill test. The Sponsor disagreed, stating that learning is not a period effect. Dr. Freidlin replied that the treatment and learning effects are mixed and that learning effect seems to be different in different treatment groups. Dr. Hung said that his interpretation of the study was,

- There is some treatment effect and a possibly differential learning effect, **or**
- It is purely a treatment effect.

The Sponsor suggested discussing the data with their clinical colleagues.

Ms. Karp stated that site 710 of Study 3033 was audited again, looking at data integrity, exercise equipment, and source documents. She said that there was no evidence indicating investigator bias and the findings will be submitted to the Division within the next few weeks.

Signature minutes preparer: _____
Meg Pease-Fye

Concurrence, Chair: _____
James Hung, Ph.D.

RD:
Hung 9.09.03
Friedlin 9.05.03

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

/s/

Margaret Pease-Fye
9/10/03 08:58:34 AM
CSO

These minutes were signed off by Dr. Hung on 9.09.03 and faxed to the sponsor on 9.10.03.

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Transmitted to FAX Number:	(650) 494 - 8769
Attention:	**Ms. Carol Karp**
Company Name:	CV Therapeutics
Phone:	(650) 384 - 8875
Subject:	Minutes from the August 11, 2003 telecon
Date:	8/13/03
Pages including this sheet:	3

From: **Meg Pease-Fye**
Phone: **301-594-5312**
Fax: **301-594-5494**

You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

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Minutes of a Teleconference

Date of teleconference: August 11, 2003

Product: Ranexa (ranolazine) 375 and 500mg extended release Tablets
Application: NDA 21-526
Sponsor: CV Therapeutics

Purpose: To discuss reviewer comments

Attendees

Division of Cardio-Renal Drug Products
Valeria Freidlin, Ph.D., Statistics, HFD-710
Jim Hung, Ph.D., Team Leader, Statisitics, HFD-710
Meg Pease-Fye, Regulatory Health Project Manager, HFD-110

CV Therapeutics
Michael Crager, Ph.D., Senior Director, Biostatistics
Margaret Dillon, Ph.D., Senior Director, Regulatory Affairs
Carol Karp, Vice President, Regulatory Affairs
Whedy Wang, M.P.H., Ph.D., Executive Director, Biometrics
[redacted] Consultant, Statistician

Background
A discipline review letter was sent to the sponsor on July 16, 2003 and a teleconference was held on July 18, 2003 both to give the Sponsor an indication of the Agency reviewer's concerns about the pending application. This telecon is one in a series of telecons to go over these issues in efforts to resolve them.

Meeting
Dr. Hung identified the two key issues as being 1) the treatment by period interactions and, 2) the period effects. Specifically, the Agency wished to discuss table ET-13A from CV Therapeutics' submission of June 17, 2003. Dr. Hung acknowledged that we must take into account the variability of the data before we can reach a conclusion, but he finds some of the data troublesome. He asked the Sponsor to provide an explanation for the reason behind the differential period effects, and an explanation of why the training effect, if that explains the period effects, should account for the clinical benefit. Relative to the possible presence of carryover effect, the Sponsor replied that the half-life of ranolazine is short and is almost completely gone by 24 to 48 hours after treatment has stopped. The exercise part of the study takes place on the seventh day so there is no reason to expect a pharmacological carry over effect. Further, they argue that treatment effect estimates are determined after they are adjusted for period effect. The Sponsor believes that the duration of exercise gets longer after every treatment period, showing improvement. This is a GLM fit, and the model includes patient, period, and treatment. They explain that table ET-13A is from a GEE analysis which adjusts out for patient effects.

Dr. Hung reiterated his concerns that table ET-13A shows worrisome consistent patterns that all three doses show much larger period effects than placebo, that seemed to show larger training, learning effects, or something else, with ranalozine. Recognizing the large between-patient variability in the data, the Agency is concerned with the consistent numeric pattern. The Sponsor suggested a graphic interpretation

of the data, suggesting that a graph will focus on patient-period differences, not on treatment differences. Residuals should shed light on the carryover, if there is any carryover effect present. Dr. Hung asked that if the model captures this effect, why does the table show that large consistent troublesome pattern in the ranolazine group? The Sponsor responded that the treatment effect is not contraindicated over period effect, that there is a difference between treatments. There was no big disagreement that there is probably no carry-over effect, but the Sponsor must ascertain the period effect and treatment by period interactions The Sponsor offered to look further, perform further analyses, and to think about ways to explain the data in table ET-13A.

The next issue discussed was Trial 3033 and specifically, site 710. Dr. Hung stated that this site was a potential outlier. The Sponsor disagreed, stating that other sites saw larger treatment differences, but that the statistical significance was higher with this site due to its larger sample size. They suggested that table 4, in the August 6, 2003 submission, addressed this variation, using the model containing treatment by center interactions as being random effects. Dr. Hung asked if there were any plans to investigate this site. The Sponsor replied that they looked at factors, including demographics, and found the site consistent with the overall patient population. Dr. Freidlin commented that this is exactly what makes this site so suspicious. If everything is the same, what accounts for the significant result? The Agency recommended that the site be inspected. The Sponsor believes that the combination of the great treatment effects differences along with the large sample size accounts for the result and that this site is no more unusual than the other sites, which is why they did the mixed model. The Sponsor agreed to go back and look at records, particularly to insure that blinding methods were intact. Dr. Hung requested the documentation concerning the inspections be submitted to the Agency. The Sponsor agreed.

Signature minutes preparer: _____
Meg Pease-Fye

Concurrence, Chair: _____
Jim Hung, Ph.D.

RD:

Hung	8.12.03
Friedlin	8.12.03

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

/s/

Margaret Pease-Fye
8/13/03 10:40:50 AM
CSO

Dr. Hung signed off on these minutes on August 13, 2003 and were faxed to the Sponsor on the same day.

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Transmitted to FAX Number:	(650) 494 - 8769
Attention:	**Ms. Carol Karp**
Company Name:	CV Therapeutics
Phone:	(650) 384 - 8875
Subject:	Minutes from the August 7, 2003 Biopharm telecon
Date:	8/19/03
Pages including this sheet:	4

From: **Meg Pease-Fye**
Phone: **301-594-5312**
Fax: **301-594-5494**

You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

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Minutes of a Teleconference

Date of teleconference:	August 7, 2003
Product:	Ranexa (ranolazine) 375 and 500mg extended release Tablets
Application:	NDA 21-526
Sponsor:	CV Therapeutics
Purpose:	To discuss reviewer comments

Attendees

Division of Cardio-Renal Drug Products
Patrick Marroum, Ph.D., Team Leader, Clinical Pharmacology and Biopharmaceutics, HFD-860
Peter Hinderling, M.D., Ph.D., Clinical Pharmacology and Biopharmaceutics, HFD-860
Nhi Nguyen, Pharm.D., Pharmacometrics, HFD-860
Atul Bhattaram, Ph.D., Clinical Pharmacology and Biopharmaceutics, HFD-860
Jogarao Gobburu, Ph.D., Team Leader, Pharmacometrics, , HFD-860
Meg Pease-Fye, Regulatory Health Project Manager, HFD-110

CV Therapeutics
Hisham Abdallah, M. Pharm, Ph.D., Senior Director, Clinical Pharmacology
Margaret Dillon, Ph.D., Senior Director, Regulatory Affairs
Markus Jerling, M.D., Ph.D., Vice President, Clinical Research
Carol Karp, Vice President, Regulatory Affairs
Dawn Parsell, Ph.D., Regulatory Affairs

Background
A discipline review letter was sent to the sponsor on July 16, 2003 and a teleconference was held on July 18, 2003 to give the Sponsor an indication of the Agency reviewer's concerns about the pending application. This telecon is one in a series of telecons to go over these issues in efforts to resolve them.

Meeting
It was agreed to go over the issues listed in the discipline review letter, sent from the Division on July 17, 2003. The issues have been cut and pasted from the letter and bolded for ease and reference.

1a) The ETT efficacy of ranolazine at trough following administration of 500 mg to 1500 mg bid was not consistently demonstrated in the pivotal trials. Hence, the time duration of ranolazine's ETT efficacy is not defined and the adequacy of the bid regimen is questionable.

Agency: The circadian rhythm of the PK of ranolazine and the drug interaction between diltiazem and ranolazine are likely to have confounded the analysis of extent and time duration of the exercise performance improving effect of ranolazine in both pivotal trials.

Ranolazine is subject to a circadian rhythm resulting on average in 20 % lower concentrations and consequently smaller ETT effects at the evening trough than at the morning trough. However, the ETTs were conducted at the morning trough in both pivotal trials, when the ranolazine concentrations and effects were greater. Thus, the extent of the effect on ETT at the evening trough and consequently the time duration of the antianginal effect of ranolazine are not unknown.

Because of a drug interaction with ranolazine, the patients on background therapy with diltiazem 180 mg qid had a 40% increase in the plasma concentrations of ranolazine in Study CVT 3033 and consequently had greater effects on ETT at both trough concentrations than patients with other background therapies.

Sponsor: The ETTs were performed in the morning, because the angina threshold is lower in the morning than in the evening. Because the ETTs were not performed in the evening, the actual values of the ETT durations are not known. Diltiazem decreased only the linear part of the oral clearance by 40% so that the reduction of the total oral clearance is smaller.

Agency: These questions relate to the uncertainty about the least effective concentration and dose of ranolazine. In Study CVT 3031, a concentration of 846 ng/ml at trough was claimed to be associated with statistically significant activity, whereas in e.g. Study RAN1514 peak ranolazine concentrations of 2131 ng/ml showed no statistically significant activity.

Sponsor: The latter study used the IR formulation.

Agency: How long it would take after initiation of a bid treatment with ranolazine 500 mg to achieve a statistically significant effect on ETT?

Sponsor: 3 days.

1b) The respective relationships between the ranolazine plasma concentrations and the effect on ETT in males and females are characterized by significantly different slopes. In women, the slope is about 33% of the slope in males. This finding suggests that the magnitude and, consequently, the time duration of the ETT effect vary between males and females. An equal dosage interval in males and females may not be adequate. ETT efficacy in females may be too limited to offset the risk posed by the QTc prolongation.

Sponsor: The ETT duration values in females are subject to a greater true variation than in males. Good response to ranolazine in females is evidenced by the significant decrease in nitrate consumption. Thus, the gender difference in the ETT values is an artifact and there should not be an important difference in the benefit from ranolazine between males and females.

Agency: Given the greater variation on the ETT values in females, would it not have been prudent to include more women in the pivotal trials?

Sponsor: The same conclusions would have been reached for women.

2) As compared to other populations, a steeper ranolazine plasma concentration to QTc relationship was found to be notable in patients with liver impairment. What is the basis for assuming that the risk in patients with mild and moderate hepatic impairment is significantly different?

Agency: The sponsor conducted a population analysis of the relationship between ranolazine concentration and effect on QTc. However, surprisingly, the patients with hepatic impairment were not included in that analysis.

Sponsor: There was concern that the sample size of the patients with liver impairment is too small for identification of important co-variates in this population.

Agency: the Agency performed a population analysis of the ranolazine concentration to ΔQTc relationship that included the patients with hepatic impairment. The patients with mild and moderate impairment displayed an approximately 3 fold steeper slope of the linear ranolazine concentration-ΔQTc relationship than subjects with normal liver function.

Sponsor: Requested a summary of the analysis performed by the Agency, and the Agency agreed to send this information to the Sponsor.

3) Ranolazine is a racemic drug. The similarity of the efficacy and safety of the individual enantiomers would justify the development of such a racemic drug. A difference in pharmacological activity and/or toxicity between the enantiomers results in patients receiving ineffective or toxic drug molecules when a racemic drug is administered. Adequate demonstration of similar efficacy and safety of the individual enantiomers was not provided for ranolazine.

Sponsor: Study RAN90 indicated that the PK of the enantiomers of ranolazine is similar.

Agency: There is agreement on the absence of stereospecificity in the PK of ranolazine. However, the issue is what evidence there is for a similarity of the PD of the enantiomers.

Sponsor: Agrees generically that this is an issue. The preclinical data-base should provide an answer.

The Agency requested additional information on the activity of CVT 4786 that is one of the four major circulating metabolites.

Signature minutes preparer: Meg Pease-Fye 8.19.03
Meg Pease-Fye

Concurrence, Chair: 8/19/2003
Patrick Marroum, Ph.D.

Drafted 8.08.03 Finaled 8.19.03

RD:

Marroum	8.12.03
Hinderling	8.12.03
Bhattaram	8.12.03
Gobburu	8.12.03
Nguyen	8.12.03

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Transmitted to FAX Number:	(650) 494 - 8769
Attention:	Ms. Carol Karp
Company Name:	CV Therapeutics
Phone:	(650) 384 - 8875
Subject:	Minutes from the August 1, 2003 telecon
Date:	8/28/03
Pages including this sheet:	3

From: **Meg Pease-Fye**
Phone: **301-594-5312**
Fax: **301-594-5494**

You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

PLEASE LET ME KNOW YOU RECEIVED THIS. THANK YOU!

Minutes of a Teleconference

Date of teleconference: August 1, 2003

Product: Ranexa (ranolazine) 375 and 500mg extended release Tablets
Application: NDA 21-526
Sponsor: CV Therapeutics

Purpose: To discuss September's Advisory Committee meeting

Attendees

Division of Cardio-Renal Drug Products

Douglas C. Throckmorton, M.D., Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D., Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Shari Targum, M.D., Medical Officer, HFD-110
Maryann Gordon, M.D., Medical Officer, HFD-110
Valeria Freidlin, Ph.D., Statistics, HFD-110
Elizabeth Hausner, D.V.M., Pharmacology, HFD-110
John Koerner, Ph.D., Pharmacology, HFD-110
Peter Hinderling, M.D., Ph.D., Clinical Pharmacology and Biopharmaceutics, HFD-860
Nhi Nguyen, Pharm. D., Clinical Pharmacology and Biopharmaceutics, HFD-860
Atul Bhattaram, Ph.D., Clinical Pharmacology and Biopharmaceutics, HFD-860
Nallaperumal Chidambaram, Ph.D., Chemistry, HFD-810
Zelda McDonald, Chief, Project Management Staff, HFD-110
Meg Pease-Fye, Regulatory Health Project Manager, HFD-110

CV Therapeutics

Luiz Belardinelli, M.D., Vice President, Drug Research and Pharmacological Sciences
Brent Blackburn, Ph.D., Senior Vice President, Drug Discovery and Pre-Clinical Development
Margaret Dillon, Ph.D., Senior Director, Regulatory Affairs
Heather Fraser, Ph.D., Scientist, Pharmacological Sciences
Carol Karp, Vice President, Regulatory Affairs
Kwan Leung, Ph.D., Senior Director, Pre-Clinical Development
[ ] , Toxicology Consultant

Background

Ranolazine SR is being developed for treatment of chronic angina in patients with severe coronary artery disease in whom other anti-anginals are inadequate or not tolerated. We alerted the Sponsor to our intention of taking ranolazine before the Advisory Committee by telecon (July 7, 2003). Separately, a Discipline Review letter was sent to the Sponsor on July 17, 2003 identifying specific concerns. Another telecon (July 18, 2003) was held to assist the Sponsor with clarification of review issues. The Sponsor believes they do not have enough time to respond to the reviewers and to create a briefing document for the committee. The Sponsor has sent in a submission outlining their intent to submit additional materials to the NDA, materials they believe may constitute a major amendment that would push back the due date by three months and provide an opportunity for the drug to go before the December Advisory Committee. This telecon was scheduled at the Agency's request to discuss the proposed cancellation of the Advisory Committee meeting in September.

Meeting

After introductions, the Sponsor remarked that their efforts to respond to the discipline review letter and to the reviewers was leaving too little time to prepare an adequate presentation to the advisory committee. They also noted that all materials would need to be in to the Advisors and Consultants in less than three weeks from the date of this telecon, and they have not yet had communications with all the reviewers, making the Sponsor unable to focus on a briefing package. Dr. Throckmorton concurred that the cancellation of the Advisory Committee would be preferable to going before the committee going before the committee when the Agency and the sponsor were not yet in agreement on the shape of the issues to be discussed.

The Sponsor then asked whether they could submit a major amendment to extend the goal date 90 days, allowing a December committee meeting. Dr. Throckmorton made it clear that decisions about goal dates and future Advisory Committee meetings would not be determined at this time. In terms of the major amendment and the subsequent goal date extension, the Division cannot comment until the amendment has been submitted and the contents have been reviewed. The Sponsor reiterated that they had both new clinical (a renal study) and non-clinical data analyses. Dr. Throckmorton replied that everyone should still plan on a 10-month review clock because the Agency has not yet seen the submission, and its contents may not constitute a major amendment. After the amendment is submitted, Dr. Throckmorton and the reviewers will determine if there is rationale for more time, thereby adding 90 days to the clock. Further, the issues raised in the discipline review letter as well as any other issues identified by the reviewers may be resolvable without the assistance of an Advisory Committee, such that the need for an Advisory Committee will be considered at a later date as well.

Everyone agreed that the September Advisory Committee would be cancelled.

Signature minutes preparer: Meg Pease-Fye 8.28.03
Meg Pease-Fye

Concurrence, Chair: 8.28.03
Douglas C. Throckmorton, M.D.

Drafted 8.5.03 Finaled 8.28.03

RD:

N. Chidambaram	8.08.03	J. Gobburu	8.18.03
E. Hausner	8.18.03	M. Gordon	8.18.03
J. Koerner	8.18.03	S. Targum	8.26.03
P. Hinderling	8.18.03	N. Stockbridge	8/28/03
N. Nguyen	8.18.03	Z. McDonald	8/28/03
A. Bhattaram	8.18.03	D. Throckmorton	8/29/03

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Transmitted to FAX Number:	(650) 494 - 8769
Attention:	**Ms. Carol Karp**
Company Name:	CV Therapeutics
Phone:	(650) 384 - 8875
Subject:	Minutes from the July 31, 2003 telecon (Pharmacology)
Date:	8/27/03
Pages including this sheet:	3

From: **Meg Pease-Fye**
Phone: **301-594-5312**
Fax: **301-594-5494**

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Minutes of a Teleconference

Date of teleconference: July 31, 2003

Product: Ranexa (ranolazine) 375 and 500mg extended release Tablets
Application: NDA 21-526
Sponsor: CV Therapeutics

Purpose: To discuss reviewer comments

Attendees
Division of Cardio-Renal Drug Products
Elizabeth Hausner, D.V.M., Pharmacology, HFD-110
John Koerner, Ph.D., Pharmacology, HFD-110
Meg Pease-Fye, Regulatory Health Project Manager, HFD-110

CV Therapeutics
Luiz Belardinelli, M.D., Vice President, Drug Research and Pharmacological Sciences
Brent Blackburn, Ph.D., Senior Vice President, Drug Discovery and Pre-Clinical Development
Margaret Dillon, Ph.D., Senior Director, Regulatory Affairs
Carol Karp, Vice President, Regulatory Affairs
Kwan Leung, Ph.D., Senior Director, Pre-Clinical Development
[ ] Toxicology Consultant
Heather Fraser, Ph.D. Scientist, Pharmacological Sciences

Background
A discipline review letter was sent to the sponsor on July 16, 2003 and a teleconference was held on July 18, 2003 to give the Sponsor an indication of the Agency reviewer's concerns about the pending application. This telecon is one in a series of telecons to go over these issues in efforts to resolve them.

Meeting
It was agreed to discuss issues from the discipline review letter and then from the July 25th telecon.

Dr. Hausner asked about ranolazine's mechanism of action. She suggested a possible mechanism is a calcium channel blocker, although it is unclear whether this is the primary mechanism. Ranolazine also appears to be a powerful negative ionotropic agent *in vivo* in anesthetized dogs, but the Sponsor indicated that this issue was explored clinically and found to be of no consequence. In general,there was a distinct lack of ECG data in the pharmacology and toxicology studies . The sponsor suggested they could provide ECG data from 6 or 12 month canine toxicology studies to address drug effects on ECG parameters. The agency agreed this could be useful.

Ranolazine appears to affect several different receptors and the Sponsor needs to rule out the contribution of different receptors to ranolazine's mechanism of action. The Sponsor believes the mechanism involves the fatty acid oxidation but is reconsidering this. The Agency requested the Sponsor's line of reasoning ruling out other possible mechanisms.

Ranolazine appears to bind α_1 and β_1 adrenergic receptors. Functional antagonism at these receptors could account for negative ionotropic effects observed *in vivo*. The sponsor indicated that β_1 binding results are inconsistent, and suggested that negative ionotropic effects are due to drug effects downstream

to adrenergic receptors, but did not provide convincing data to support this view. The Agency recommended that the sponsor screen the top eleven major metabolites, parent drug and enantiomers for β_1 adrenergic and opioid receptors binding affinity, and additionally evaluate these molecules for effects on contractility in cardiac tissue, *in vitro*. For all studies, the agency requested concurrent controls be evaluated. The sponsor agreed to perform these studies.

Signature minutes preparer: Meg Pease-Rye
Meg Pease-Rye

Concurrence, Chair: Elizabeth Hausner
Elizabeth Hausner, D.V.M.

Drafted 8.11.03 Finaled 8.19.03
RD:
Hausner 8.18.03
Koerner 8.18.03

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Transmitted to FAX Number:	(650) 494 - 8769
Attention:	**Carol Karp**
Company Name:	**C.V. Therapeutics**
Phone:	(650) 384 - 8875
Subject:	**Dr. Freidlin's table**
Date:	**July 23, 2003**
Pages including this sheet:	3
From:	**Meg Pease-Fye**
Phone:	**301-594-5312**
Fax:	**301-594-5494**

As explained in the teleconference on Friday, July 18, 2003 this table was made from the raw data in Table 2.10.0 in study 3031.

As requested by Dr. Freidlin, please submit detailed calculations demonstrating power for the test of carry-over effect and the test for treatment by period interaction.

Please let me know you received this.

2 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(4) Draft Labeling

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Transmitted to FAX Number:	(650) 494 - 8769
Attention:	Ms. Carol Karp
Company Name:	CV Therapeutics
Phone:	(650) 384 - 8875
Subject:	Minutes from the July 18, 2003 telecon
Date:	7/28/03
Pages including this sheet:	5

From: **Meg Pease-Fye**
Phone: **301-594-5312**
Fax: **301-594-5494**

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Minutes of a Teleconference

Date of teleconference: July 18, 2003

Product: Ranexa (ranolazine) 375 and 500mg extended release Tablets
Application: NDA 21-526
Sponsor: CV Therapeutics

Purpose: To discuss reviewer comments

Attendees

Division of Cardio-Renal Drug Products
Norman Stockbirdge, M.D., Ph.D., Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Shari Targum, M.D., Medical Officer, HFD-110
Maryann Gordon, M.D., Medical Officer, HFD-110
Valeria Freidlin, Ph.D., Statistics, HFD-110
Elizabeth Hausner, D.V.M., Pharmacology, HFD-110
Peter Hinderling, M.D., Ph.D., Clinical Pharmacology and Biopharmaceutics, HFD-860
Atul Bhattaram, Ph.D., Clinical Pharmacology and Biopharmaceutics, HFD-860
Nallaperumal Chidambaram, Ph.D., Chemistry, HFD-810
Zelda McDonald, Chief, Project Management Staff, HFD-110
Meg Pease-Fye, Regulatory Health Project Manager, HFD-110

CV Therapeutics
Hisham Abdallah, M. Pharm, Ph.D., Senior Director, Clinical Pharmacology
Luiz Belardinelli, M.D., Vice President, Drug Research and Pharmacological Sciences
Brent Blackburn, Ph.D., Senior Vice President, Drug Discovery and Pre-Clinical Development
Michael Crager, Ph.D., Senior Director, Biostatistics
Margaret Dillon, Ph.D., Senior Director, Regulatory Affairs
Colin Hislop, M.D. Vice President, Clinical Research
Markus Jerling, M.D., Ph.D., Vice President, Clinical Research
Carol Karp, Vice President, Regulatory Affairs
Louis Lange, M.D., Ph.D., Chairman and Chief Executive Officer
Kwan Leung, Ph.D., Senior Director, Pre-Clinical Development
[ ] Toxicology Consultant
Whedy Wang, M.P.H., Ph.D., Executive Director, Biometrics
Andrew Wolff, M.D., Senior Vice President Clinical Research and Development

Background
Ranolazine SR is being developed for treatment of chronic angina in patients with severe coronary artery disease in whom other anti-anginals are inadequate or not tolerated. A telecon was held on July 7, 2003 alerting the Sponsor to our intention of taking ranolazine before the Advisory Committee. In preparation, a discipline review letter was sent to the Sponsor on July 17, 2003 identifying specific review concerns. The Agency requested this teleconference to assist the Sponsor with clarification of these issues prior to going before the Advisory Committee in September, 2003.

Meeting

Safety: The Sponsor requested a definition for threshold with respect to the concentration-related increases in the mean QT/QTc interval. The reviewers are concerned about outliers, specifically at peak effect and not at trough. The Sponsor understood, and had also already sent in a submission addressing the second safety issue.

Statistics: The Sponsor asked for clarification of concerns referring to study 3033. The Agency explained that the p-value becomes not significant when the outlier is excluded. When asked if this was linked specifically to site 710, the Agency replied that, yes, site 710 seems to carry the trial.

Referring to a specific table 2.10.0 in volume 146 of the application, treatment effects for trial 3031 showed they depended on the period and on the treatment in the prior period. The first period was very different from the later periods. Additionally, the reviewer believed that the study was not planned to test treatment-by-period interaction or carry-over effect. The Agency requested specific power calculations for the test of differential carry-over and test of treatment-by-period interaction. The Sponsor agreed to submit a detailed explanation justifying their conclusions. The Sponsor suggested a separate telecon be held with the medical officers and statisticians.

Efficacy: The Sponsor suggested removing the proposed labeling indications from the package going before the Advisory Committee, and prepare to show ranolazine's safety and efficacy data. The Agency agreed that this would be a good strategy, and suggested that the committee might give a recommendation concerning the Sponsor's pursuit of a second line therapy. Further, Dr. Stockbridge noted that in past discussions with the Sponsor, the Agency advised them to perform a study to look at effects in resistant populations. Instead, the Sponsor believed that an alternative trial of 4000 patients could be conducted post-marketing. The Agency will draft questions for second-line therapy and the Advisory Committee will determine if this strategy is acceptable.

Clinical Pharmacology: The Agency reviewer echoed the concerns about efficacy at trough. As a result of a cirrcadian rhythm, the trough concentrations of ranolazine are higher in the morning than in the evening. The anti-anginal effects were routinely measured in the morning in the pivotal trials and this may have affected the outcome. The co-administration of diltiazem in trial 3033 increased the plasma concentrations of ranolazine by 40% thereby increasing the extent and time duration of the anti-anginal effect.

The slope of the relationship of the ranolazine plasma concentration and the anti-anginal effect in women is significantly smaller than in men indicating that the extent and time duration of the anti-anginal effect is importantly smaller in the female population.

The increased slope of the relationship between ranolazine plasma concentration and QT interval in patients with mild and moderate hepatic impairment was at issue. In contrast to the sponsor's analysis the Agency's analysis shows that the slope is increased similarly in both populations. The Sponsor maintained that in mildly hepatically-impaired patients, there is little increase in the slope; however, in moderately impaired patients, they believe the slope is clearly increased and these patients should not be exposed to ranolazine.

The final clinical pharmacology concern was the paucity of evidence that the two enantiomers of ranolazine have identical pharmacodynamics. Given that the PK of the enantiomers are similar differences in the pharmacodynamic between the enantiomers would indicate unnecessary loading of future patients with toxic or inert drug. The sponsor indicated that they would like to address some of these issues further and would provide additional information.

Pharmacology/Toxicology: The Sponsor stated that they were aware of the difficulty in ascribing the effects of ranolazine to fatty acid oxidation. They will submit a statement concerning fatty acid oxidation, acknowledging that the mechanism of action is as yet unknown; however, the evidence should be able to point to a dominant mechanism. Pre-clinical data indicate that ranolazine is a calcium channel blocker. Insufficient clinical data were submitted concerning effects on cardiac ion channels. This issue will undergo further discussion between the Sponsor and the Agency.

Clarification was requested for the receptor binding and metabolite characterization. The Agency responded that non-target receptor adverse effects had been seen non-clinically. The metabolites could be produced in significant amounts and therefore the contribution of the metabolites to the toxicity profile should be investigated. The Sponsor said they would submit additional information before the briefing documents are sent to the Advisory Committee. The Agency also noted that minimal data were submitted and that the histological data were both inconsistent and incompletely reported. For example, uterine weight had shown drug-related changes in two species but with no histologic data reported. Also, in one dog study, sperm production and testicular morphology were specifically noted for control animals, but the same data were not reported for drug treated animals.

The Sponsor then asked some general questions. The first concerned site 710 and its impact on carry-over effects. The Sponsor asked if this issue will be resolved prior to the Advisory Committee meeting or if this will be one of the questions asked of the committee. The Agency replied that the issue will not be resolved between now and the meeting. If there is no agreement about the interpretation of results, it will be put before the committee.

As in previous discussions, the Sponsor again brought up their plan to start a large 4000 patient long-term safety study looking at patients initially presenting with acute coronary symptoms and will include angina. They asked if it would be helpful to provide the Advisory Committee with a detailed proposal of the study. They also asked if a commitment to do the trial would help get the drug approved now for a limited indication that could be expanded later. Dr. Stockbridge responded that submitting a protocol would not help in getting a regulatory decision now. It may be advantageous only if the Sponsor believes it would help make their case to the Committee. The Sponsor asked if it would annoy the Division if they submitted it. Dr. Stockbridge encouraged the sponsor to do so, if that would help get the trial started sooner. He emphasized, however, that submitting the protocol would not get a new commitment from the Agency about what implications this trial would have in terms of approval of ranolazine in this review period.

It was agreed that there should additional telecons for statistics/clinical, pharmacology/toxicology and clinical pharmacology, and concerning the 4000 patient study. Also, the chemistry reviewer will call the Sponsor and add his comments the following week.

Signature minutes preparer: Meg Pease-Fye 7.28.03
Meg Pease-Fye

Concurrence, Chair: Norman Stockbridge 7/28/03
Norman Stockbridge, M.D., Ph.D.

Drafted 7.21.03 Finaled
RD:
Stockbridge 7.28.03

Targum	7.25.03
Gordon	7.24.03
Freidlin	7.25.03
Hausner	7.23.03
Hinderling	7.23.03
Bhattaram	7.23.03
Chidambaram	7.21.03
McDonald	7.21.03

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Transmitted to FAX Number:	(650) 494 - 8769
Attention:	**Ms. Carol Karp**
Company Name:	CV Therapeutics
Phone:	(650) 384 - 8875
Subject:	Minutes from the July 7, 2003 telecon
Date:	7/10/03
Pages including this sheet:	3

From: **Meg Pease-Fye**
Phone: **301-594-5312**
Fax: **301-594-5494**

You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

PLEASE LET ME KNOW YOU RECEIVED THIS. THANK YOU!

Minutes of a Teleconference

Date of teleconference:	July 7, 2003
Product:	Ranexa (ranolazine) 375 and 500mg extended release Tablets
Application:	NDA 21-526
Sponsor:	CV Therapeutics
Purpose:	To discuss the potential of ranolazine going in front of the Advisory Committee in September, 2003

Attendees

Division of Cardio-Renal Drug Products

Douglas C. Throckmorton	Director, Division of Cardio-Renal Drug Products, HFD-110
Zelda McDonald	Chief, Project Management Staff, HFD-110
Meg Pease-Fye	Regulatory Health Project Manager, HFD-110

CV Therapeutics

Carol Karp	Vice President, Regulatory Affairs
Margaret Dillon	Senior Director, Regulatory Affairs
Andrew Wolff, M.D.	Senior Vice President Clinical Research and Development
Louis Lange, M.D., Ph.D.	Chairman and Chief Executive Officer
Sandra Skettino, M.D.	Vice President, Clinical research and operations

Background

Ranolazine SR is being developed for treatment of chronic angina in patients with severe coronary artery disease in whom other anti-anginals are inadequate or not tolerated. The Agency requested this teleconference to discuss ranolazine going before the Advisory Committee in September, 2003.

Meeting

While recognizing that the initial data reviews were not yet complete, Dr. Throckmorton said that he and Dr. Temple agreed that an Advisory Committee for ranolazine would be beneficial for both the Agency and the Sponsor. The Sponsor commented that, although the company expected an Advisory Committee, they were concerned about having sufficient dialogue(s) with the Agency prior to the meeting in September.

The Sponsor had spoken with Dr. Stockbridge, and was interested in understanding the reviewer's concerns over the efficacy of ranolzine in angina, as they thought that had been established. With regard to the effects of ranolazine at trough, they agreed that one of the pivotal studies (a cross-over study) had issues with regard to potential carry-over effects, but their statisticians had not seen any evidence for that. Dr. Throckmorton said that this could not be resolved in this phone call, but agreed it was a central issue, and encouraged the Sponsor to talk directly to the reviewers as the outcomes appeared to be data-driven. In terms of showing efficacy in resistant populations, the Sponsor's case that ranolazine works when other therapies do not would need to be discussed with the Advisory Committee.

In terms of safety, in order to overcome the reviewer's concerns about the QT interval prolongation, Dr. Throckmorton thought there were three potential avenues:

- prove that QT prolongation is not a concern
- agree that there is a safety concern, but that it can be managed, or
- agree there is a concern but show that the added benefit of ranolazine outweighs the safety risks

The Sponsor requested Agency feedback and dialogue several times during the meeting. The Sponsor also requested additional time to prepare, suggesting extending to the December meeting. Since the goal date is in October, moving the meeting to December is not an option for the Division. The Sponsor was reassured the Division would offer as much dialogue as possible to help them prepare for the meeting in September.

The Sponsor described areas they believed needed further discussion. The first was to determine whether a study of anti-anginal benefits in refractory patients was the only option. They are in the process of a large 4000 patient trial studying acute coronary syndrome, which is expected to show significant safety data and ranolazine's anti-anginal effects. The Sponsor proposed submitting this study as a post-marketing commitment. Dr. Throckmorton responded that a large trial has the potential to give additional efficacy data, but is likely to be different from standard anti-anginal assessments conducted by the sponsor to date. If the trial is an outcome trial showing ranolazine saves the lives of heart failure patients, the argument could be made that benefit offsets the risk of QT prolongation. The timing of the submission would be something that would have to be discussed at another time.

The Sponsor also described the pre-clinical safety characteristics as unique and compelling, that the phenotype of QT could prove clinically meaningful, but was concerned that they had not heard the Agency's views. Dr. Throckmorton replied that the Agency had not reached any conclusions with regard to the potential for 'good' QT prolongation, but that we could certainly ask the Committee their views when the sponsor presents their arguments. Dr. Throckmorton said he would talk with the pre-clinical reviewers about the pre-clinical data. To date, he had not heard their final assessment.

Action Items

Dr. Throckmorton will notify the Advisors and Consultants team about taking ranolazine before the Advisory Committee in September 2003.

Dr. Throckmorton will talk with the review team and encourage them to discuss any issues they have with the sponsor as appropriate. In particular, additional discussions on the cross-over study would be useful.

One goal of the interactions between the FDA and the sponsor should be to have concurrence on the data (numbers), if not the interpretation of those numbers, so there will be no disagreement during the Advisory Committee meeting.

The Sponsor will start thinking about presenting at the Advisory Committee meeting and planning preparatory telecons and/or meetings with the Division.

Ms. Pease-Fye will schedule time on the Calendar for a series of telecons/meetings with the Sponsor.

Signature minutes preparer: Meg Pease-Fye 7.9.03

Meg Pease-Fye

Concurrence, Chair:

Douglas C. Throckmorton, M.D.

Drafted 7.08.03 Finaled 7.09.03

RD:

McDonald 7.09.03

Throckmorton 7.09.03

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Transmitted to FAX Number:	(650) 858-0390
Attention:	Dr. Margaret Dillon
Company Name:	CV Therapeutics
Phone:	(650) 475-9628
Subject:	**Minutes of Meeting w/FDA, October 10, 2002** **IND 43,735** **Ranolazine SR Tablets**
Date:	November 14, 2002
Pages including this sheet:	**5**
From:	**Edward Fromm**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Minutes of a Meeting between CV Therapeutics and the FDA

Date: October 10, 2002

Sponsor: CV Therapeutics

Subject: IND 43,735
Ranolazine SR Tablets

Type of Meeting: Pre-NDA Meeting

FDA Participants:

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research
Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Thomas Marciniak, M.D., HFD-110, Medical Officer
James Hung, Ph.D., HFD-710, Statistician/Team Leader
Charles Le, Ph.D., HFD-710, Statistician
Albert DeFelice, Ph.D., Pharmacology Team Leader
Elizabeth Hausner, D.V.M, HFD-110, Pharmacologist
John Koerner, Ph.D, HFD-110, Pharmacologist
Angelica Dorantes, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Jogarao Gobburu, Ph.D., HFD-860, Pharmacometrics Team Leader
Mehul Desai, M.D., HFD-110, Medical Officer (pre-meeting only)
Salma Koessel, M.P.H., M.D., HFD-110, Medical Officer (pre-meeting only)
Edward Fromm, HFD-110, Regulatory Health Project Manager

Office of Drug Safety

Cindy Kortepeter, Pharm.D., HFD-430, Safety Evaluator, DDRE
Susan Lu, R.Ph., HFD-430, Team Leader, DDRE
Victor Raczkowski, M.D., HFD-400, Director, Office of Drug Safety
Julie Beitz, M.D., HFD-430, Division Director, DDRE
Sandra Birdsong, HFD-430, Regulatory Health Project Manager, DDRE
Denise Toyer, Pharm.D., HFD-420, Team Leader, DMETS
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Luiz Belardinelli, M.D., Ph.D., Vice President, Drug Research and Pharmacological Sciences
Brent Blackburn, Ph.D., Vice President, Drug Discovery & Pre-Clinical Development
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Markus Jerling, M.D., Ph.D., Vice President, Clinical Research (Clinical Pharmacology)
Carol D. Karp, Vice President, Regulatory Affairs
Sandra L. Skettino, M.D., Vice President, Clinical Research and Operations
Whedy Wang, Ph.D., Senior Director, Biometrics
Andrew A. Wolff, M.D., F.A.C.C., Senior Vice President, Clinical Research & Development

Consultants

Jeremy N. Ruskin, M.D., Associate Professor of Medicine, Cardiac Arrhythmia Service, Massachussetts General Hospital

Background

Ranolazine SR is being developed for the treatment of chronic angina, principally in combination with other anti-anginal therapies. At a meeting on August 13, 2002, the Agency identified several topics that needed follow-up from the sponsor. These were:

- Identification of the anti-anginal indication, perhaps narrower than originally planned, that would be supported by available efficacy data.
- Submission of data from clinical studies conducted with both immediate and sustained-release ranolazine supporting the efficacy of the drug in patients already receiving maximal doses of conventional anti-anginal drugs (beta-blockers or calcium-channel blockers).
- The need for additional safety data because the drug is a new chemical entity and has been associated with prolongation of the QT interval. The sponsor could also submit data from preclinical studies arguing that the mechanism of action of ranolazine is different from other drugs that are known to prolong the QT interval

CV Therapeutics plans on submitting their NDA by December 2002.

Meeting

Dr. Throckmorton opened the meeting by noting that the sponsor proposes to limit the use of the drug to patients that are resistant to conventional anti-anginal therapies or patient populations that are intolerant to available treatments. We have reviewed the sponsor's proposals and have the following comments:

Patients Resistant to Conventional Anti-Anginal Treatment

Dr. Throckmorton said we are not convinced that patients have received maximal doses of beta-blockers and/or calcium channel blockers in the data submitted to date and therefore are hesitant about labeling these patients as "resistant". Dr. Temple noted that the average dose of amlodipine appears to be about 6 mg/day, nowhere near the maximally approved dose of 10 mg/day. Calcium channel blockers, in particular, have been shown to have greater efficacy with higher doses.

CV Therapeutics replied that they believe that ranolazine, as an add-on therapy, has been shown to have a statistically significant effect on angina when patients were being treated with adequate doses of conventional therapies. They believe that doses of beta-blockers and calcium channel blockers used in the studies mirror "real world" prescribing of these drugs by physicians. Dr. Temple said because of the potential safety risks associated with the drug, we need reassurance that the drug would be used only after patients have received the highest approved doses of beta-blockers and calcium channel blockers. To help convince us that the doses of conventional agents used in the studies were, in fact, "maximal", the sponsor will need to show (e.g., from the literature) that doses used were close enough to the highest approved dose so that very little additional clinical benefit could be expected. Dr. Temple noted however, that it would still be a difficult argument to make because of the relatively small numbers of patients in the studies. Dr. Throckmorton said the sponsor could augment their case by submitting information documenting why the patients were taking a particular dose of beta-blocker or calcium channel blocker in the studies.

Intolerant Patients

Dr. Temple noted that the sponsor's definition of intolerant patients (i.e, those with low blood pressure, bradycardia, diabetes, heart failure, PR interval prolongation, and bronchospasm) is too broad and needs to be redefined and restricted to patients who should definitely not use other approved therapies. It is reasonably clear that patients with bronchospasm should not get beta blockers [Added after meeting: note recent NEJM meta analysis showing good tolerability of selective beta blockers in people with reactive airway disease] but the use of beta blockers in patients with diabetes should not always be discouraged. CV Therapeutics replied that they agree that diabetics would be the least specific population but said that the drug should be indicated for those patients who have COPD (Chronic Obstructive Pulmonary Disease) and heart failure. Dr. Temple said that there is some evidence to suggest that patients with bradycardia and heart failure are more predisposed to arrhythmias and therefore we will need data showing that ranolazine is not harmful to these populations as well as other fragile populations that are clearly intolerant to other drugs. The sponsor said that they have these data and they will be submitted with the NDA application. Moreover, they note that nonclinical and clinical studies have shown that the drug does not have an adverse effect in bradycardic subjects. In patients who would be expected to be more predisposed to arrhythmias (i.e., those with increased sympathetic tone), the drug was found to have no arrhythmogenic effects.

Safety Data and Post-Marketing Study

CV Therapeutics noted that they would have additional 500 patient-years of safety data that will be submitted at the NDA 4-month safety update. Dr. Throckmorton said these data would be reassuring but said that additional safety data would be needed. Ideally, this information would come from a controlled trial in angina patients comparing ranolazine and a calcium channel blocker. This trial could be done post-approval and could lead to the drug being indicated as a first line treatment for angina.

Dr. Temple said the sponsor should think about a Risk Management Plan to be implemented for this drug if and when it is approved. A Medication Guide will likely be needed and also some type of post-marketing study to determine that the drug is being used appropriately (e.g., as second-line therapy).

Drug Interaction (ketoconazole) Study

Dr. Throckmorton said that it appears that the QT interval prolongation is somewhat modest at dosing of 500 and 1000 mg twice daily but increases more significantly at 1500 mg twice a day. Our concern is that a drug like ketoconazole, when given to patients using the sponsor's proposed dosing range of 500-1000 mg twice daily, may produce ranolazine concentrations more likely to cause substantial QT prolongation. In addition, there appears to be a difference in the dose of ranolazine for QT prolongation in normal volunteers and patients with angina. Therefore another study, for example, of ranolazine 1000 mg twice a day and 400 mg of ketoconazole would be helpful. The sponsor said they have not seen any evidence of a difference between normal volunteers and angina patients with regard to QT interval prolongation. Dr. Temple said that the sponsor should contact the Biopharmaceutics reviewer for the application to clarify the differences.

Ranolazine vs. Sotalol Study

The sponsor said that in preclinical studies it has been demonstrated that ranolazine produces a QT interval prolongation by a mechanism that is different from other drugs, such as sotalol. In fact, they believe that ranolazine can reverse some of sotatlol's QT effects. CV Therapeutics said they were thinking about conducting a study with ranolazine and sotalol in cardiac patients and asked if this study would help alleviate the Agency's concerns about the safety of the drug. Dr. Throckmorton replied that although this study would be helpful, he suggested that the sponsor focus its efforts on obtaining data for the resistant or intolerant populations.

NDA Submission

CV Therapeutics asked if the data that has been summarized today was enough for a NDA submission. Dr. Temple replied that the application would probably be fileable, although a final determination cannot be made until the application is submitted. He said that it appears that without another study, an indication for the drug's use in resistant patients is unlikely. An indication for specific, intolerant populations is more likely as long as data can be provided that adequately supports the safety of the drug in these subgroups.

Summary of Main Action Items

- The sponsor submitted a summary of the data that they believe show that the drug is efficacious when used as an add-on to adequate doses of conventional anti-anginal therapy. Dr. Temple said that for the drug to be approved for use in resistant populations it must be shown that approximately maximal doses of beta blockers and calcium channel blockers have been used. This case has yet to be made, although he suggested ways of obtaining more persuasive evidence.

- The sponsor presented examples of patients who are intolerant to conventional anti-anginal therapies and should be candidates for ranolazine therapy. Dr. Temple said that the intolerant subgroups would need to be redefined to include only those patients who are clearly intolerant to conventional therapy and not those who the physician may have some concern about using. He also said that safety data would be needed for these subgroups to show that ranolazine is not inherently harmful to these populations.

- The application will probably be fileable, although it is not yet clear how likely it is that the dataset would support approval of the NDA.

- Additional controlled safety data will be needed to better quantify the drug's arrhythmogenic potential, although it is possible this information could be obtained post approval. A Risk Management Plan and Medication Guide will also be needed for this drug. A post-marketing study may be needed to show that the drug is being used appropriately (e.g., as second-line therapy).

Minutes Preparation: _____
Edward Fromm

Concurrence: _____
Robert Temple, M.D.

dr/10-11-02/11-7-02/11-12-02

Rd: LStephens-10/23/02
MLee-10/24/02
DToyer-10/24/02
SBirdsong-10/24/02
JBeitz-10/24/02
VRaczkowski-10/26/02
SLu-10/28/02
CKortepeter-10/28/02
SKoessel-10/28/02
MDesai-10/28/02
JGobburu-10/30/02
ADorantes-10/30/02

JKoerner-10/31/02
EHausner-10/31/02
ADeFelice-10/31/02
CLe-10/31/02
JHung-11/1/02
TMarciniak-11/4/02
AKarkowsky-11/6/02
NStockbridge-11/6/02
DThrockmorton-11/7/02

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/s/

Edward Fromm
11/14/02 11:03:58 AM
Dr. Temple signed the minutes on November 14, 2002.

Minutes of a Meeting between CV Therapeutics and the FDA

Date: August 13, 2002

Sponsor: CV Therapeutics

Subject: IND 43,735
Ranolazine SR Tablets

Type of Meeting: Guidance

FDA Participants:

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research
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Thomas Marciniak, M.D., HFD-110, Medical Officer
Albert DeFelice, Ph.D., Pharmacology Team Leader (pre-meeting only)
Elizabeth Hausner, D.V.M, HFD-110, Pharmacologist
John Koerner, Ph.D, HFD-110, Pharmacologist
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Jogarao Gobburu, Ph.D., HFD-860, Pharmacometrics Team Leader
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Salma Koessel, M.P.H., M.D., HFD-110, Medical Officer (pre-meeting only)
Edward Fromm, HFD-110, Regulatory Health Project Manager

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Brent Blackburn, Ph.D., Vice President, Drug Research & Pre-Clinical Development
Margaret Dillon, Ph.D., Senior Director, Regulatory Affairs
Colin Hislop, M.D., Vice President, Clinical Research (Ranolazine)
Markus Jerling, M.D., Ph.D., Vice President, Clinical Research (Clinical Pharmacology)
Carol D. Karp, Vice President, Regulatory Affairs
Sandra L. Skettino, M.D., Vice President, Clinical Research and Operations
Whedy Wang, Ph.D., Senior Director, Biometrics
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Consultants

Craig M. Pratt, M.D., Director, Clinical Research, Baylor College of Medicine
Jeremy N. Ruskin, M.D., Associate Professor of Medicine, Cardiac Arrhythmia Service, Massachussetts General Hospital

Background

Ranolazine SR is being developed for the treatment of chronic angina, principally in combination with other anti-anginal therapies. The meeting today is to discuss efficacy and safety information on ranolazine as well as the sponsor's progress on characterizing the QT prolongation associated with the drug. CV Therapeutics plans on submitting a NDA by December 2002.

Meeting

CV Therapeutics opened the meeting be giving an overview of the safety and efficacy data accumulated since the last meeting with the Division on July 25, 2000. They noted the following:

- 5 efficacy trials have been conducted with the drug that show that a statistically significant effect on angina symptoms.
- The drug does not increase mortality in a high-risk population. The annual event rate was 2.4 %, which represents 12 events.
- The QT prolongation appears to be about 2-4 msec per 1000 ng/ml concentration of ranolazine. The sponsor describes this increase as of "uncertain clinical significance". Concentrations above 8000 ng/ml were achieved in a very small percentage of study patients; this may correlate to about a 20 msec QT prolongation. Generally, dizziness and nausea occur in a small percentage of the patients at normal dosing levels (500 to 1000 mg/bid) and a CNS syndrome at much higher concentrations (e.g., 8000 ng/ml).

  Dr. Temple asked about Figure 1 (Relationship Between Changes in QTc from Baseline and Model-Predicted Ranolazine Concentrations) on page 38 of the briefing document and why the regression line did not go through 0. The sponsor replied that the line did not go through 0 because there was some negative placebo effect. They noted that the slope is just about the same with their method versus going through the 0 intercept.

- In pre-clinical studies, the drug does not appear to induce early afterdepolarizations (EADs) associated with prolongation of the repolarization phase of the action potential. They believe that EADs can lead to Torsades de Pointes (TdP) and ventricular arrhythmias. The sponsor noted that ranolazine reduced EADs caused by quinidine and sotalol in their animal models.

Agency's Suggestions for Clinical Development (Safety)

Dr. Temple said that an 8-10 msec increase in the QT interval (based on 1000 mg/bid dosing) is somewhat disconcerting, especially given the modest safety database accumulated to date for the drug. The safety database for a drug representing a new class that could potentially be used in a broad population has to be more complete. He suggested that the sponsor conduct a trial in about 2000 angina patients (those that are still having angina even though treated with other agents) and have as a control group those patients that are currently taking a beta blocker (atenolol) or a calcium channel blocker. The goal of the study would be to monitor the rates of the more severe adverse events.

CV Therapeutics asked when would the safety data need to be submitted. Dr. Temple said we prefer to have these data prior to submission of the NDA; however, if the sponsor decides on a more restrictive indication, the need for the safety study could be lessened. Alternatively, the sponsor could submit arguments (e.g., the electrophysiological mechanism of QT prolongation of ranolazine is different from other drugs removed from the market) as to why the safety study is not needed. He noted however, that because several drugs with QT prolongation have been removed from the market it is our strong preference to have more safety information for the drug prior to the submission of the NDA.

CV Therapeutics noted that the drug Ziprasidone had a unique mechanism of action different from other anti-psychotic drugs and was approved even though it has QT interval prolongation. They asked if the safety burden for ranolazine could be lessened due to its unique mechanism of action compared with other anti-anginal patients. Dr. Temple replied that Ziprasidone is indicated for

treatment of psychosis, a debilitating illness. Angina does not on its face represent a similarly serious problem and risks are less acceptable.

Agency's suggestions for Clinical Development (Efficacy)

Dr. Temple noted that in the CARISA (Combined Assessment of Ranolazine in Stable Angina) study, patients did not receive an adequate dose of amlodipine, atenolol, and diltiazem and therefore interpretation of ranolazine's effect as an add-on to these therapies is difficult. The sponsor agreed that the doses of the background therapy were not maximal, but said this was done to minimize the cardiac type side effects that could occur with these drugs. Dr. Temple suggested that another study be conducted in anginal patients that are being treated with an adequate dose of a calcium channel blocker or combination of a calcium channel blocker and atenolol with nitrate background therapy. The study should be stratified and use a 1000 mg twice daily dose of ranolazine.

CV Therapeutics said they had completed a study with the immediate release form of ranolazine in 150 patients, 80-90 of whom were on calcium channel blockers. They said that exercise test results from that study showed that ranolazine was just as beneficial as atenolol in improving exercise duration during the study. Dr. Temple asked what was the definition of exercise duration. The sponsor replied that exercise duration was defined as the timepoint in which a patient could no longer continue the test.

Dr. Temple said the immediate release study results could provide assurance to the Agency that the drug is effective as an add-on to conventional anti-anginal therapy, but noted the sponsor would need to provide information on the doses of calcium channel blockers used in the study. The sponsor affirmed that they will submit information on patient subsets that are resistant to background therapy. Dr. Temple encouraged the sponsor to submit these data prior to the submission of the NDA so as to enable discussion of an acceptable indication for the drug.

Conclusion

CV Therapeutics said that they believe that patients with angina are not being treated appropriately and said ranolazine has been proven to be effective in treating angina both as a monotherapy and as an add-on to conventional anti-anginal therapies. They acknowledge the QT interval prolongation of the drug but believe its benefits outweigh the potential risks.

Dr. Temple said additional data are needed to verify the efficacy of the drug; the sponsor could conduct another study with ranolazine as an add-on to adequate doses of a calcium channel blocker or beta blocker or could submit analyses of data already collected that show that the drug works when added to anginal patients receiving adequate/maximal doses of conventional therapy.

Dr. Temple said the QT prolongation is a concern to the Agency, and we believe that additional safety data are needed. Our preference is that these data be collected from a study in several thousand patients to see how the drug compares to a beta blocker or calcium channel blocker for serious adverse events.

Dr. Temple encouraged the firm to meet with the Agency before submitting their NDA to discuss the sponsor's progress in collecting additional safety and efficacy data for the drug as well as to the indication the company wishes to pursue.

Minutes Preparation:

Edward Fromm

Concurrence:

Robert Temple, M.D.

dr/8-21-02/8/28/02/8-29-02

Rd: SKoessel-8/21/02
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Transmitted to FAX Number:	(650) 858-0390
Attention:	Ms. Margaret Dillon
Company Name:	CV Therapeutics
Phone:	(650) 475-9628
Subject:	**Minutes of Telecon w/FDA, February 14, 2002** **IND 43,735** **Ranolazine SR**
Date:	February 19, 2002
Pages including this sheet:	**3**
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Minutes of a Telecon between CV Therapeutics and the FDA

Date: December 20, 2001

Sponsor: CV Therapeutics

Subject: IND 43,735
Ranolazine SR

Type of Telecon: Pre-NDA Discussion

FDA Participants:

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Maryann Gordon, M.D., HFD-110, Medical Officer
Elizabeth Hausner, D.V.M., HFD-110, Pharmacologist
John Koerner, Ph.D., HFD-110, Pharmacologist
James Hung, Ph.D., HFD-110, Statistician/Team Leader
Angelica Dorantes, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
Edward Fromm, HFD-110, Project Manager

CV Therapeutics (CVT)

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Patricia Hirano, Manager, Regulatory Affairs
Colin Hislop, M.D., Vice President, Clinical Research – Ranolazine
I-Zu Huang, M.D., Associate Director, Clinical Research
Markus Jerling, M.D., Ph.D., Executive Director, Clinical Research (Clinical Pharmacology)
Bernarr Pardo, Senior Director, Data Management
Sandra Skettino, M.D., Vice President, Clinical Research and Operations
Whedy Wang, Ph.D., Senior Director, Biostatistics
Andrew Wolff, M.D., F.A.C.C., Senior Vice President, Clinical Research and Development

Background

Ranolazine SR is being developed for the treatment of chronic angina, both alone and in combination with other anti-anginal therapies. The sponsor recently completed CARISA (Combination Assessment of Ranolazine in Chronic Angina), the second of two pivotal efficacy trials that they believe shows ranolazine achieved statistically significant increases over placebo for the primary endpoint of exercise duration at trough plasma concentrations of the drug.

Based on these results, CVT is planning to submit an NDA in the 3rd quarter of 2002 and is seeking guidance on how to organize the different elements of their upcoming submission.

Telecon

Dr. Throckmorton noted that the Division in previous discussions with the sponsor had discussed the apparent QT prolongation and carcinogenic effects of the drug and therefore would not focus on these concerns during this telecon. CVT said they were well aware of these concerns and would ask for a meeting in the first quarter of 2002 to specifically discuss the Division's concerns about the QT prolongation of the drug.

Missing CRF's

Before addressing the questions proposed by the sponsor in their background package, the Division asked for clarification on the 194 CRF's (Case Report Forms) that were reported as missing by the sponsor. The sponsor said that at the present time 194 CRF's from 16 studies (by the previous sponsor, Syntex) have not been located and they asked for a waiver for submitting these at the time of the NDA submission. Because of the safety concerns associated with the drug, Dr. Throckmorton said the Division would not grant this waiver. If the CRF's were not submitted with the NDA (or not enough of them to make a determination of safety), the Division might refuse to file the application. The sponsor said they would let the Division know as soon as possible how many CRF's they could locate.

Dr. Throckmorton asked if the sponsor had narrative summaries (death, SAEs (serious adverse effects), and dropouts) for patients in the studies. The sponsor replied that they had narratives for all patients that had a SAE, death or dropped out of the studies. They added that they would have final study reports for all patients at the time of NDA submission.

Sponsor's Questions

GENERAL CONSIDERATION

CVT believes that their overall development program adequately addresses drug-drug interactions, pharmacokinetics, safety and efficacy of ranolazine SR tablets. It is planned that further discussions regarding specific safety issues, including CVT's methodology and analysis for QT/risk assessment will occur and are currently targeted for 1Q2002.

In general, does the Agency concur with the overall development program? Dr. Throckmorton said that because of the apparent QT prolongation of the drug and other safety concerns, the Division would have to review the data submitted at the time of NDA submission before giving a more definitive answer.

CVT asked if the Division would focus on ranolazine data obtained for immediate-release form of the drug (by Syntex) or the sustained release form, developed by CVT. Dr. Throckmorton said that in general, the proposed formulation for marketing data is more relevant, and the immediate release data would be of most relevance for safety.

GENERAL PLAN FOR INTEGRATED SUMMARY OF SAFETY

As described on pages 18-19 and 56 of the briefing document and in the fax (refer to page 6 of the attached fax), CVT proposes that the integrated summary of safety (ISS) will focus on those studies that evaluated a dose $\geq$ 120 mg. The sponsor noted that every study that had a least one patient that received 120 mg would be included in the ISS. Dr. Throckmorton said the overall plan for the ISS was acceptable but had the following comments:

- As stated above, CRFs are needed for all patients who experienced a serious adverse event, died, or prematurely withdrew from a study.
- It appears that ranolazine will have an adequate amount of long-term safety/exposure data at the time of NDA submission, but the Division will have to review the data before making a final determination of whether enough long-term safety data have been submitted.
- The sponsor should inform the Division, at the time of NDA submission, of any blinded studies involving ranolazine that are ongoing.
- The COSTART v5.0 coding of safety data by body system and preferred term employed by the previous sponsor and retained by CVT for consistency was acceptable.
- Line listings of COSTART SAEs do not need a second ISS.

GENERAL PLAN FOR INTEGRATED SUMMARY OF EFFICACY

CVT is developing ranolazine SR tablets for the following target indication: Ranolazine is indicated for the treatment of chronic angina pectoris. Ranolazine can be used alone or in combination with other anti-anginal agents, including beta-blockers, nitrates and calcium channel blockers.

Is the proposed scope of the ISE acceptable to support this target indication? Dr. Throckmorton said a determination of efficacy could not be made until the NDA was submitted and reviewed. He said the sponsor's overall plan was acceptable but noted the following:

- There appears to be little experience with ranolazine in patients with different anti-anginal therapies. The sponsor replied that some patients are currently on 2 or 3 anti-anginal medications in open-label trials and said that there would be a lot of safety data from patients taking different combinations of anti-anginal agents.

OTHER PLANNED CLINICAL INFORMATION

1. Are the overall contents of the following Clinical sections acceptable for:
   - Item 6: Human Pharmacokinetics and Bioavailability Section?
   - Item 8: Clinical Data Section?
   - Item 10: Statistical Section?
   - Item 11: Case Report Tabulations?
   - Item 12 Case Report Forms?
   - Item 19: Financial Information?

   Dr. Throckmorton said the proposed outline was acceptable but said that Biopharmaceutics reviewer, Dr. Dorantes, had specific suggestions as to the format and content of the Human Pharmacokinetics and Bioavailability section. Mr. Fromm will send her suggestions to the sponsor as soon as possible.

   The Financial Disclosure by Clinical Investigators criteria proposed by the sponsor appear to be acceptable; the medical reviewer of the NDA application will review the Financial Disclosure data when the NDA is submitted.

2. For the majority of studies conducted with ranolazine, CVT plans to provide full clinical study reports. For the studies listed in the table on page 5 of the attached fax, CVT plans to provide only abbreviated study reports.

Is this proposed approach to submission of reports (full or abbreviated) acceptable? Dr. Throckmorton said this was acceptable but noted that reviewers of the NDA may ask for additional information as needed.

3. CVT proposes to submit all clinical trial data for all 64 studies included in the Integrated Safety Database to meet the requirements of Item 11, Case Report Tabulations (CRTs). These data will be submitted as SAS datasets, by domain, closely following the CDISC standards. CVT's adoption of the CDISC standards should facilitate reviewer access to the data, and is consistent with the FDA Patient Profile Viewer initiative (66 FR 237, December 10, 2001). Therefore CVT proposes not to include patient profiles as part of this submission and asked the Division if this was acceptable. Dr. Throckmorton said it was acceptable not to send in the patient profiles and that the CDISC format for the CRTs was acceptable.

Carcinogenicity Studies

The sponsor asked if the Carcinogenicity Assessment Committee (CAC) would evaluate the carcinogenicity study results that were recently submitted. Dr. Hausner said that the Executive CAC would review the carcinogenicity studies on January 15, 2002 but noted that, as previously discussed, historical laboratory control data were still needed for the carcinogenicity studies.

Summary of Main Action Items

- The sponsor will let the Division know in a timely manner how many of the 194 missing CRFs it is able to locate.
- The carcinogenicity study reports submitted by the sponsor will be reviewed by the Executive CAC on January 15, 2002. The lack of historical control data for the carcinogenicity studies may be problematic.
- CVT plans on submitting the NDA in the 3rd quarter of 2002.
- Dr. Dorantes will provide her requested format for the Biopharmaceutics section to Mr. Fromm to convey to the sponsor.

Minutes Preparation: _____
Edward Fromm

Concurrence: _____
Douglas Throckmorton, M.D.

dr/ef-12-28-01/1-08-02

Rd: EHausner-1-2-02
JKoerner-1-2-02
ADorantes-1-2-02
JHung-1-3-02
MGordon-1-2-02
NStockbridge-1-4-02
DThrockmorton-1-4-02
NMorgenstern-1-7-02

Appears This Way
On Original

Updated List of Questions and Supporting Information

GENERAL CONSIDERATION

1. CVT believes our overall development program adequately addresses drug-drug interactions, pharmacokinetics, safety and efficacy of ranolazine SR tablets. It is planned that further discussions regarding specific safety issues, including CVT's methodology and analysis for QT/risk assessment will occur and are currently targeted for 1Q2002.

   In general, does the Agency concur with the overall development program?

GENERAL PLAN FOR INTEGRATED SUMMARY OF SAFETY

1. As described on pages 18-19 and 56 of the briefing document and in this fax (refer to page 6 of this fax), CVT proposes that the integrated summary of safety (ISS) will focus on those studies which evaluated a dose ≥ 120 mg.

(a) Is the proposal to provide descriptive summaries for all patients who experienced a serious adverse event, died, or prematurely withdrew from a study because of an adverse event acceptable?

(b) Is the proposal to integrate the safety data for the 64 studies which met the criteria listed on page 19 of the briefing document and listed in Table 2 (page 21) acceptable?

(c) Is the proposed ISS outline, provided in Attachment 1 of the briefing document acceptable?

(d) Is the overall format of the sample ISS appendices tables acceptable?

2. Is the proposed approach to perform an analysis on the Integrated Safety Database as well as the four subcategories described on pages 13 and 22-25 of the briefing document acceptable?

3. It is expected that the NDA will contain data from studies conducted with ranolazine involving approximately 3000 subjects or patients who received at least one dose of study medication. As described in the briefing document on page 18, the original NDA for ranolazine SR tablets will include approximately 400 patients who have received ranolazine SR tablets for ≥ 6 months and approximately 200 patients who have received ranolazine SR tablets for ≥ 12 months. In addition, approximately 200 patients received ranolazine IR for ≥ 6 months and approximately 200 patients received ranolazine IR ≥ 12 months.

   Does the Agency agree that there will be an adequate amount of long-term safety/exposure data included in the original NDA submission for ranolazine SR tablets?

4. Two studies are expected to be ongoing at the time of NDA submission: open-label safety studies CVT 3032 and CVT 3034. It is estimated that an additional 200 patients will be exposed to ranolazine in the CVT 3034 study who will not be included in the original NDA submission. Therefore, CVT proposes that the 4-month safety update be submitted in the form of an update to the ISS database containing the following new information (since the NDA cut-off date of 15 October 2001):

- data listings for patients participating in the ongoing, open-label, long-term safety studies CVT 3032 and CVT 3034 who have died, experienced a serious adverse event or withdrawn from the studies due to an adverse event.
- datasets for patients participating in the in the ongoing, open-label, long-term safety studies CVT 3032 and CVT 3034 who meet the above criteria.
- Case Report Forms (CRFs) for any patient participating in CVT 3032 or CVT 3034 who has died or dropped out of study due to an adverse event

For any blinded study which may be ongoing at the time of NDA submission, CVT proposes that the following information be provided in the 4-month safety update:

- Blinded data listings for all patients who died, experienced a serious adverse event or withdrew from the study due to an adverse event, irrespective of causality.

Does the Agency agree with this proposal?

5. The coding of safety data utilized by Syntex during the latter portion of their development program for ranolazine was by COSTART body system and preferred term. For consistency, CVT has coded all adverse events by COSTART body system and preferred term using a CVT-modified COSTART version 5.0 dictionary. The following modifications have been made to the COSTART version 5.0 dictionary in the CVT-modified COSTART dictionary:

   Changes with respect to mappings to COSTART terms:

COSTART v5.0 term	CVT-modified COSTART term
CORONARY ART DIS	ANGINA PECTORIS
COR PULM	HEART FAIL
HEART FAIL LEFT	HEART FAIL
HEART FAIL RIGHT	HEART FAIL

   Changes with respect to mappings to Body System:

COSTART v5.0 term	COSTART v5.0 Body System	CVT-modified Body System
EDEMA	MAN	CV
EDEMA GENERAL	BODY	CV
EDEMA GENERAL	MAN	CV
EDEMA PERIPH	MAN	CV

   The coding of all relevant Syntex- and CVT-conducted studies reported and summarized in the integrated summary of safety will be coded from the verbatim term to the CVT-modified COSTART version 5.0 dictionary body system and preferred term. This coding will be used for the original NDA and all subsequent updates to the NDA which include safety information.

   Is this acceptable?

GENERAL PLAN FOR INTEGRATED SUMMARY OF EFFICACY

1. CVT is developing ranolazine SR tablets for the following target indication: Ranolazine is indicated for the treatment of chronic angina pectoris. Ranolazine can be used alone or in combination with other anti-anginal agents, including beta-blockers, nitrates and calcium channel blockers.

   Is the proposed scope of the ISE acceptable to support this target indication?

2. Is the proposed plan to utilize data from the 12 studies described in Section 4 of the briefing document to support the overall efficacy, dosing recommendations, continued efficacy, and withdrawal effects of ranolazine acceptable?

3. Is the proposed plan to not integrate study data from these studies, with the exception of a concentration response analysis, acceptable?

4. Is the proposed outline for the ISE provided in Attachment 2 of the briefing document acceptable?

OTHER PLANNED CLINICAL INFORMATION

1. Are the overall contents of the following Clinical sections acceptable for:
   - Item 6: Human Pharmacokinetics and Bioavailability Section?
   - Item 8: Clinical Data Section?
   - Item 10: Statistical Section?
   - Item 11: Case Report Tabulations?
   - Item 12 Case Report Forms?
   - Item 19: Financial Information?

2. For the majority of studies conducted with ranolazine, CVT plans to provide full clinical study reports. For the studies listed in the table below, CVT plans to provide only abbreviated study reports. The rationale for providing abbreviated study reports for these studies is included in this table.

Protocol No. **Briefing Document Ref.**	**Rationale for Providing Abbreviated Report**
RAN002 (CL 3689) Vol 2, p. 044	Early, low dose pharmacokinetic study in 18 healthy male volunteers for which the database is not available. This study is not included in the proposed Integrated Safety Database as stated in Section 3.4 of the briefing document.
RAN007 (CL 5819) Vol. 2, p. 079	Early, low dose, dose finding study in 12 males with ischemic heart disease for which the database is not available. This study is not included in the proposed Integrated Safety Database as stated in Section 3.4 of the briefing document.
RAN008 (CL 4058) Vol. 2, p.44	Early, low dose pharmacokinetic study in 18 healthy male volunteers for which the database is not available. This study is not included in the proposed Integrated Safety Database as stated in Section 3.4 of the briefing document.
RAN059 (CL 5863) Vol. 2, p. 034	Relative bioavailability study for the immediate-release formulation carried out in six healthy male volunteers.
RAN1490 (CL5250) Vol. 2, p. 100	Study in patients with chronic stable angina that was terminated early due to slow enrollment after 12 patients had been recruited.

Protocol No. Briefing Document Ref.	Rationale for Providing Abbreviated Report
RAN2240 (CL 6940) Vol. 2, p. 106	Exploratory study to examine if ranolazine prolongs the time to first revascularization. This study was terminated after 11 patients were enrolled.
RAN2302 (CL 6958) Vol. 2, p. 107	Exploratory study to examine the effectiveness of ranolazine in patients with intermittent claudication. Such use/indication is not the subject of this NDA.
RAN2320 (CL 7044) Vol. 2, p. 108	Exploratory study to examine the effectiveness of ranolazine in patients with intermittent claudication. Such use/indication is not the subject of this NDA. This study was terminated after only 3 patients had been enrolled.

Is this proposed approach to submission of reports (full or abbreviated) acceptable?

3. CVT proposes to submit all clinical trial data for all 64 studies included in the Integrated Safety Database to meet the requirements of Item 11, Case Report Tabulations. These data will be submitted as SAS datasets, by domain, closely following the CDISC standards. CVT's adoption of the CDISC standards should facilitate reviewer access to the data, and is consistent with the FDA Patient Profile Viewer initiative (66 FR 237, December 10, 2001). Therefore CVT proposes not to include patient profiles as part of this submission.

   (a) Is the submission of CRTs following the CDISC format acceptable?

   (b) Is the proposal to not include patient profiles acceptable?

4. CVT proposes to include in Item 12 those CRFs for patients or subjects who participated in a CVT-sponsored study with ranolazine and terminated early from a study due to an adverse event or died. These studies enrolled approximately 1000 patients and 250 subjects who received at least one dose of ranolazine SR. In addition, this includes approximately 30 subjects who received at least one dose of ranolazine injection.

   Efforts ongoing to locate the CRFs for studies sponsored by Syntex and the status of this effort are described on page 37 of the briefing document. At this time, CVT requests a waiver from submitting CRFs for the studies listed in Table 5 of the briefing document (pages 37-40). This includes nine Phase II/III Controlled Studies, three Phase II/III Uncontrolled Studies, three Special Population/Other Indication Studies, 30 Phase I and Clinical Pharmacology Studies and 16 Early/Low Dose Studies. CVT will continue to work with Roche to locate the CRFs for these studies and CVT hopes to provide all available CRFs in the original NDA for all patients or subjects who died or terminated early from a clinical trial due to an adverse event. However, we respectfully note that these CRFs may not be available. Therefore:

(a) Is the proposal for submission of CRFs for patients or subjects who participated in a CVT-sponsored study with ranolazine and terminated early from a study due to an adverse event or died acceptable?

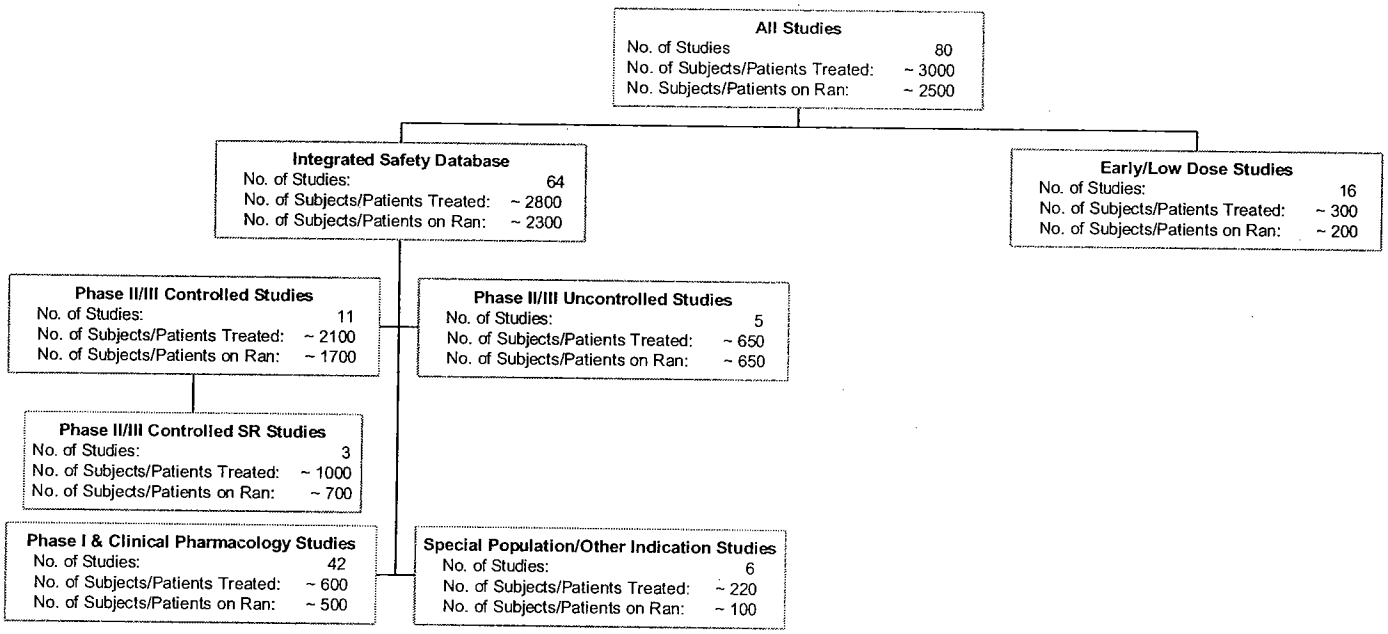
(b) The estimated number of subjects or patients from all Syntex-conducted studies that either died or withdrew from a study due to an adverse event and for which CRFs may not be available is 194.

Are waivers granted from submitting CRFs for the studies listed in Table 5 of the briefing document (pages 37-40)?

5. The criteria for identification of covered studies for the purposes of Financial Disclosure are described on page 41 of the briefing document. To meet the requirements of 21 CFR 54 – Financial Disclosure by Clinical Investigators, CVT has identified those studies which meet the criteria for covered studies.

Is the proposal to provide financial certification for those investigators participating in the studies listed on page 42 acceptable?

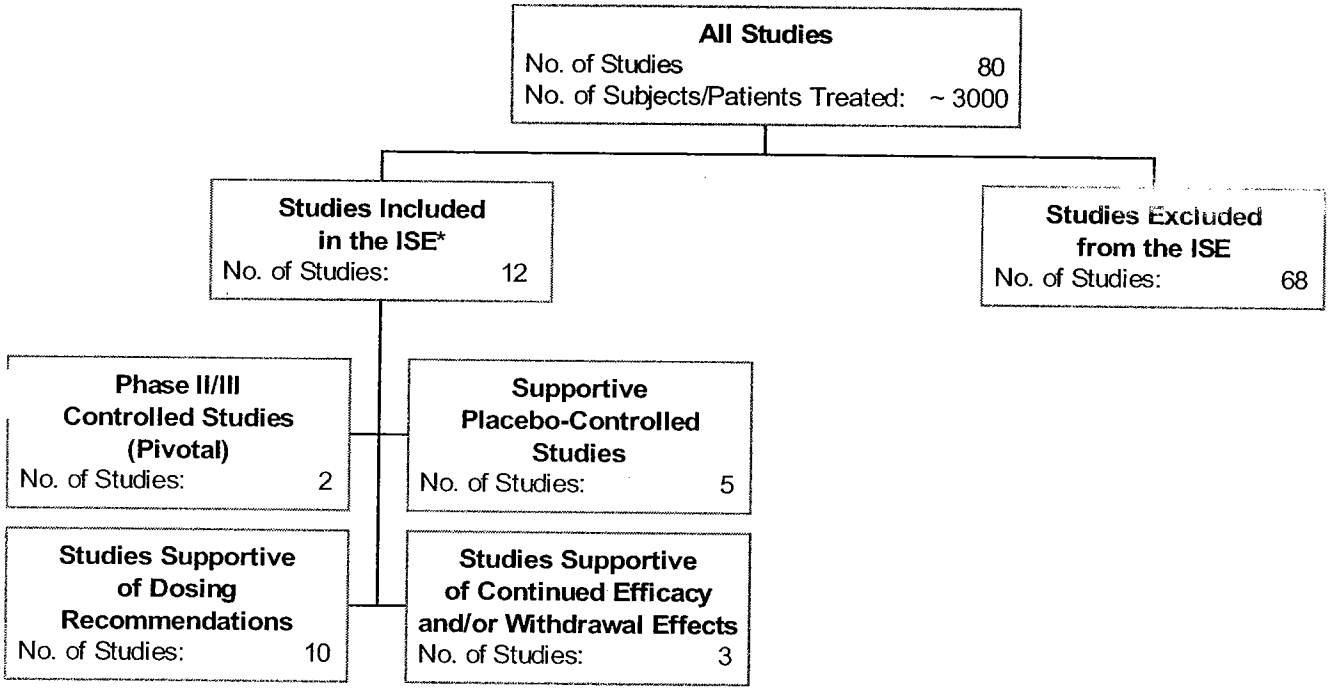
Overview of Studies Presented in the Integrated Summary of Safety



Overview of Studies to be Presented in the Integrated Summary of Efficacy

Studies were selected for inclusion in the Integrated Summary for Efficacy based on the following criteria:

- Support ranolazine IR 240 mg as the minimum effective dose in chronic angina
- Support the dosing rationale
- Provide supporting pharmacology data characterizing dose response
- Support continued efficacy and/or withdrawal effects
- Support duration of drug effect
- Studied the highest ranolazine IR dose used in chronic angina



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

/s/

Edward Fromm
1/8/02 01:16:50 PM
CSO
Dr. Throckmorton signed the minutes on January 8, 2002.

Edward Fromm
1/8/02 01:29:54 PM
CSO
Dr. Throckmorton signed the minutes on January 8, 2002.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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Transmitted to FAX Number:	(650) 858-0390
Attention:	Ms. Allene Dodge
Company Name:	CV Therapeutics
Phone:	(650) 812-9575
Subject:	**Minutes of Telecon w/FDA, Feb.27th, 2001 IND 43,735**
Date:	03/22/01
Pages including this sheet:	**5**
From:	**Edward Fromm**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

Please notify us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

Minutes of a Telecon between CV Therapeutics and the FDA

Date: February 27, 2001

Sponsor: CV Therapeutics

Subject: IND 43,735
Ranolazine SR

Type of Meeting: Discussion of proposed and ongoing pre-clinical and clinical studies

FDA Participants:

Douglas Throckmorton, M.D., HFD-110, Deputy Division Director
Norman Stockbridge, M.D., Ph.D., Medical Team Leader
Maryann Gordon, M.D., HFD-110, Medical Officer
Elizabeth Hausner, D.V.M., HFD-110, Pharmacologist
John Koerner, Ph.D., HFD-110, Pharmacologist
Angelica Dorantes, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Edward Fromm, HFD-110, Project Manager

CV Therapeutics

Luis Belardinelli, M.D., Vice President, Drug Research and Pharmacological Sciences
Brent Blackburn, Ph.D., Vice President, Drug Discovery and Pre-clinical Development
Allene M. Dodge, Senior Director, Regulatory Affairs and Quality Assurance
Patricia Hirano, Manager, Regulatory Affairs
Markus Jerling, M.D., Ph.D., Senior Director, Clinical Research
Sandra Skettino, M.D., Vice President, Clinical Research and Operations
Whedy Wang, Ph.D., Director, Biostatistics

Background

Ranolazine SR is being developed for the treatment of chronic angina, both alone and in combination with other anti-anginal therapies. The Division, in previous meetings with the sponsor, has identified QTc prolongation as a major safety concern of the drug. The sponsor requested a teleconference with the Division to obtain guidance on the design of pre-clinical and clinical studies used to gain further information on the electrophysiological properties of the drug.

Telecon

The sponsor opened the meeting by outlining the pre-clinical and clinical studies that were ongoing to obtain further information on the QT prolongation associated with the drug. Dr. Throckmorton said the Division was concerned that too much emphasis was being placed on the animal studies relative to the clinical trials in humans. He said, however, that because of the cardiac repolarization problems with the drug, information is needed on the characterization of metabolites in animals to guide the clinical plan. The firm replied that they were trying to determine the metabolites and their effects in animals so as to appropriately design clinical studies in humans. They noted that they were trying to characterize the electrophysiological effects of ranolazine by in-vitro and in-vivo methods. The firm said in general these methods were centered around finding information about ventricular repolarization, ion channel (current) flow, and using models of other known IKr blockers.
Dr. Throckmorton asked the firm how well have the human metabolites been characterized. The firm said that three metabolites have been identified with the highest concentrations in studies conducted to date. They noted that

ranolazine has been found to be metabolized by CYP3A4 and CYP2D6. The specific isoenzymes responsible for the formation of the 3 metabolites are as follows:

1. CYP3A4-metabolite 1
2. CYP2D6-metabolite 2
3. CYP3A4 and CYP2A6 (dual mechanism)-metabolite 3

Dr. Throckmorton asked the firm if they plan on characterizing any other of the metabolites of ranolazine. CV Therapeutics said that, at the present time, they did not plan on studying other metabolites (other than the top 3) in humans. Dr. Throckmorton encouraged testing with the other metabolites noting that in a recent Advisory Committee meeting for Ziprasidone, committee members asked about the characterization of all metabolites of a drug. The firm noted that the 3 (highest in concentration) metabolites of ranolazine had shown no electrophysiological effects and wondered if they should pursue further testing with these compounds. Dr. Throckmorton said that they should pursue in-vitro and in-vivo tests with these metabolites; he emphasized that the company needs to elucidate as much safety data relative to the QT prolongation of the drug as possible for the parent and any metabolites.

Drug-Drug Interaction Studies

CV Therapeutics said that a study outline of a study to further characterize possible drug-drug interactions between ranolazine and ketoconazole, a potent inhibitor of CYP3A4, will be sent in to the Division shortly. Dr. Throckmorton said that study would be helpful but said the company should also explore other potential drug-drug interactions with other enzymatic pathways, such as CYP2D6. The firm indicated that they would consider this request.

Dr. Dorantes asked if p-glycoprotein studies were planned for ranolazine. The sponsor responded that an interaction study was planned with verapamil soon and the protocol will be sent in to the Division.

Dr. Dorantes asked that any PK/PD analyses that the company plans be submitted to the Division for review and comment.

Study CVT 3111

The firm said that a study (CVT 3111) has been initiated to further characterize electrocardiographic changes associated with escalating doses of ranolazine given by continuous intravenous infusion to healthy human volunteers. They noted that plasma concentrations achieved in the study would be much higher than those expected from the maximal clinical dose (2000 mg/day). The sponsor mentioned that high doses of ranolazine were proving intolerable for a number of patients but said, nevertheless, that they were committed to having the study completed. Dr. Throckmorton said he appreciated that the firm was exploring the dose/adverse event profile of the drug and said this information would be critical in determining the safety and efficacy of the drug. For instance, demonstrating the efficacy of the drug in patients resistant to available anti-anginal therapy would provide useful data of efficacy in an under served population.

High concentration of ranolazine and shortening of the QT interval

CV Therapeutics said that they have noticed that the action potential seems to shorten with increasing concentration of the drug in in vitro studies and asked if they could demonstrate this phenomenon in clinical trials with a wide variety of doses (i.e., show a bell-shaped curve with respect to QT prolongation), would it provide reassurance to the Agency regarding the QTc problem. Dr. Throckmorton said he knows of no drug that has been able to demonstrate conclusively that a plateau develops with respect to concentration of the drug versus length of the QT interval. He noted that Ziprasidone made this claim at a recent Advisory Committee meeting but committee members were not convinced by this argument. Whether the presence of a plateau would provide assurance of safety is debatable. Dr.

Throckmorton did say, however, this information could be reassuring to the Agency with respect to potential overdose of the drug, but that predicting its value otherwise would be difficult.

Pre-clinical studies

Dr. Hausner noted that a study that the firm is conducting trying to find potential torsade de pointes in dogs with ranolazine is not a sensitive model and should use another positive control such as terfenadine instead of d-sotalol. The firm said that they felt sotalol was a proven inducer of torsades in dogs but noted that they have not encountered any torsade de pointes with ranolazine in the canine model. Dr. Koerner noted that the control drugs should be given in the same mode as the experimental agent (i.e., if the drug is given I.V. continuous infusion, then the control should be given in the same manner).

The sponsor asked the Division what animal models are preferred for testing for torsade de pointes. Dr. Koerner said the predictive power of proarrhythmic models has not been determined. Additionally, even with limited use, false negatives have occurred (terfenadine).

The sponsor asked the Division if the drug or metabolite was found to have no effect on IKr should they pursue further studies in animals. Dr. Koerner said that if the sponsor chooses to evaluate for drug effect in HERG, mammalian cell expression systems are preferable to expression in xenopus oocytes. Additionally, if ventricular myocytes are studied, IKr should be isolated from IKs.

Dr. Hausner said the firm should consider using a full range of doses when doing their in vitro studies to determine if the metabolites have activity in the test systems. Dr. Koerner noted that in-vitro concentrations are difficult to relate to in-vivo concentrations when determining the safety of a compound. The sponsor asked if no changes in action potential were seen in the dose-response studies would it be necessary to continue further testing. Dr. Koerner said that high doses need to be evaluated, and a single assay may not eliminate concern.

NDA submission

Mr. Fromm asked the sponsor what the target date was for the planned NDA submission. The sponsor said that it was planned for submission to the Division in mid-2002. Dr. Throckmorton commented that it was imperative for the sponsor to meet with Division as soon as they have information on items such as a point estimate of mortality, data from the I.V. infusion study (CVT 3111), and number of events. He emphasized that the focus of such a meeting should be both the safety and efficacy of ranolazine. The intent would be for the Agency to review and comment on the adequacy of the anticipated patient exposure data for efficacy and safety.

Conclusion

The Division offered guidance on planned and ongoing pre-clinical and clinical studies; it was emphasized that the sponsor should obtain as much safety information of ranolazine in humans, especially with respect to QT interval prolongation.
Dr. Throckmorton said it was important to meet with the Division when the broad outline of the clinical development plan for ranolazine is known.

Minutes Preparation: _____
Edward Fromm

Concurrence: _____
Douglas Throckmorton, M.D.

dr/ef-3/01/01-3/19/01

Rd: ADorantes-3/2/01
JKoerner-3/5/01
AHausner-3/5/01
MGordon-3/6/01
NStockbridge-3/6/01
DThrockmorton-3/6/01

/s/

Edward Fromm
3/21/01 09:02:50 AM

Minutes of a Meeting between CV Therapeutics and the FDA

Date: July 25, 2000

Sponsor: CV Therapeutics

Subject: IND 43,735
Ranolazine SR Tablets

Type of Meeting: Guidance

FDA Participants:

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Maryann Gordon, M.D., HFD-110, Medical Officer
Elizabeth Hausner, D.V.M, HFD-110, Pharmacologist
John Koerner, Ph.D, HFD-110, Pharmacologist
Sayed Al Habet, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Patrick Marroum, Ph.D., HFD-860, Clinical Pharmacology and Biopharmaceutics, Team Leader
Lu Cui, Ph.D., HFD 710, Biostatistician
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
Edward Fromm, HFD-110, Consumer Safety Officer

CV Therapeutics

Brent Blackburn, Ph.D., Vice President, Drug Research & Pre-Clinical Development
Allene M. Dodge, Senior Director, Regulatory Affairs and Quality Assurance
Patricia Hirano, Manager, Regulatory Affairs
Markus Jerling, M.D., Senior Director, Clinical Research
Sandra L. Skettion, M.D., Executive Director, Clinical Research and Operations
Whedy Wang, Ph.D., Director, Biostatistics
Andrew A. Wolff, M.D., F.A.C.C., Senior Vice President, Clinical Research & Development

Consultants

[ ] , Senior Statistician, [ ]

Background

Ranolazine SR is being developed for the treatment of chronic angina, both alone and in combination with other anti-anginal therapies. The firm requested a meeting with the Division to discuss key clinical and associated preclinical activities supporting a targeted 4th quarter 2001 NDA submission.

Meeting

Dr. Lipicky opened the meeting by noting that the Division has several areas of concern with the current preclinical and clinical activities supporting the ranolazine NDA submission. These are:

PreClinical

- Animal carcinogenicity studies found tumors (histiocytic sarcomas and pheochromocytomas) that appear to be dose-related
- More data is needed on the relative potency of mice versus humans; the total body burden (as reflected by AUC) is very close to that of man and indicates a narrow therapeutic margin
- There are 3 metabolites whose activity is unknown and that may be associated with carcinogenicity. Dr. Lipicky said further studies should be done on these metabolites to elucidate their activity.

The firm presented slides (see attached) discussing ongoing studies that are focused on the electrophysiological effects of ranolazine and its metabolites in animals. Drs. Koerner and Lipicky commented that the firm should obtain higher orders of magnitude in dose concentrations in their pre-clinical studies to better differentiate the safety profile of ranolazine and its metabolites in comparison to humans.

Clinical

- The drug is an IKr blocker and prolongs QTc in humans. Because a dose-dependent increase in QTc interval is a surrogate for sudden death, the hurdle for approval for the angina indication is much higher. Dr. Lipicky said ranolazine could be approved with this increased risk but that the company would have to prove that the drug is more effective than anti-anginal agents currently on the market. He suggested that without a mortality outcome trial with thousands of high-risk patients treated over several years, the company should conduct a trial with patients who are refractory to anti-anginal agents used at maximally tolerated doses. The decision as to what would constitute refractoriness would be up to the physician and the patient. Dr. Lipicky said that a large number of subjects would need to be randomized to ranolazine, the refractory anti-anginal agent or placebo. At the very least, ranolazine would have to beat the agent to which patients are refractory. Dr. Lipicky said that since excess mortality concerns with ranolazine would still be an issue, a point estimate of the mortality effect would be helpful.

  CV Therapeutics replied to Dr. Lipicky's remarks by noting that they believe that the QTc effect of ranolazine is not clear and that it may, in fact, be a false positive similar to the effect of verapamil. Dr. Lipicky noted that verapamil's effects on the QT interval are hard to measure and that verapamil is not an IK blocker like ranolazine. The firm said that they could do a historical review of all safety data collected for ranolazine and plot a survival curve based on that data. Dr. Lipicky said this review might be helpful but what is really needed are safety data from placebo-controlled trials.

  The firm said that they will conduct an IV infusion with ranolazine with escalating doses to see what side effects (particularly QT changes) are evident. Dr. Karkowsky pointed out that it was important that pharmacodynamic steady state is reached when giving the infusion and mentioned those ECG measurements, for example, at days 1,4, and 14 would be helpful in achieving that goal. The firm mentioned that the CARISA efficacy trial would measure parent and metabolite levels at the 2, 6, and 12 week timepoints and asked if they demonstrated that the parent to metabolite ratios at each of these timepoints stayed the same would that satisfy the Division's concerns about metabolites with unusually long half-lifes. Dr. Lipicky said it would.

  CV Therapeutics asked the Division if a mortality outcome trial was necessary. Dr. Lipicky remarked that if patients become intolerant before reaching the highest dose of ranolazine in the infusion study then the point-estimate for mortality would be less important. He also said that

positive results from the infusion study and other safety related studies would lessen the need for a mortality outcome trial. In this case, however, the issue would probably go to a Cardiovascular and Renal Advisory Committee meeting where some members may want safety data from a mortality outcome trial. Dr. Karkowsky noted that the firm appears to be planning a CHF trial with ranolazine and asked if mortality data could be generated from that trial. Dr. Lipicky said obtaining mortality data from the CHF trial would be acceptable and said that a safety trial could even be conducted with normal volunteers.

Efficacy Trials

CV Therapeutics said they believe that the MARISA trial has demonstrated statistically, dose-related increases in exercise duration with ranolazine. They have also started a second trial, CARISA, which is a double-blind, randomized, placebo-controlled trial testing ranolazine SR versus placebo for exercise duration in patients with chronic stable angina who are receiving a single, daily, concomitant anti-anginal medication (either diltiazem, atenolol, or amlodipine). The firm noted that the CARISA trial will run for 12 weeks and will be followed by a 48 hour randomized withdrawal period. They asked the Division, if CARISA is successful, would the two trials serve as the basis for approval on efficacy. Dr. Lipicky said that the two trials, if successful (i.e., show an absence of tolerance over time), would be acceptable for approval on efficacy. He cautioned, however, that the Division's attitude to approving drugs that induce QT prolongation is pessimistic and that this aspect of ranolazine was at the heart of a risk/benefit analysis the Division would make.

Drug-Drug Interaction Studies

Dr. Marroum said that the firm should use a more potent inhibitor of the Cytochrome P450 3A4 (CYP3A4) enzyme for its drug interaction studies and not diltiazem. The firm asked how the use of a more potent inhibitor such as ketoconazole would affect the caution statement that they already plan on having in the label regarding ranolazine and other drugs affecting the CYP3A4 enzyme. Dr. Marroum said that it could possibly lead to a contraindication instead of a caution in the labeling. Dr. Lipicky said that he prefers that ketoconazole be used as the inhibitor for the drug-drug interaction studies.

Dr. Marroum said that it would be helpful to investigate whether an inhibitor of p-glycoprotein such as verapamil would have any effects on the plasma levels of ranolazine.

Conclusion

Dr. Lipicky said that the two efficacy trials that the company is undertaking, if successful, would serve as a basis of approval on efficacy. He said, however, that ranolazine-induced QT interval prolongation remains a major concern to the Division and that the company would have to prove through animal and human studies that the clinical benefit outweighs the safety risks.

Minutes Preparation: Edward Fromm

Edward Fromm

Concurrence: Ray Lipicky

Raymond Lipicky, M.D.

dr/8-1-00/8-16-00

Rd: LCui-8/7/00
JKoerner-8/14/00
EHausner-8/15/00
PMarroum-8/15/00
AHabet-8/15/00
MGordon-8/8/00
AKarkowsky-8/8/00

cc: IND 43,735
HFD-110
HFD-110/Blount
HFD-110/EFromm/SMatthews

5 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(4) Draft Labeling

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-526		Supplement Number S-000	
Drug: **Ranexa (ranolazine) 500 mg Extended Release Tablets**		Applicant: **C.V. Therapeutics**	
RPM: **Meg Pease-Fye**		**HFD-110**	Phone # **(301) 796 - 1130**
Application Type: **(X)** 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): **Not Applicable**	

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	**1**
• Other (e.g., orphan, OTC)	Not Applicable
❖ User Fee Goal Dates	**January 27, 2006**
❖ Special programs (indicate all that apply)	**(X)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	( ) Paid
• User Fee waiver	**(X)** Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes **(X)** No
• This application is on the AIP	( ) Yes **(X)** No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	**(X)** Verified
❖ Patent	
• Information: Verify that patent information was submitted	**(X)** Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity Summary (approvals only)	February 2, 2006
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	RHPM October 23, 2003 RHPM February 1, 2006
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	Approvable October, 2003
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (X) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Not Applicable
• Most recent applicant-proposed labeling	January 27, 2006
• Original applicant-proposed labeling	July 26, 2005 (resubmission)
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	December 22, 2005 (DDMAC) December 9, 2005 (DDMAC) November 23, 2005 (DMETS) June 6, 2003 (DMETS)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Not Applicable
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Not Applicable
• Applicant proposed	July 26, 2005 (resubmission)
• Reviews	December 22, 2005 (DDMAC) December 9, 2005 (DDMAC) November 23, 2005 (DMETS) June 6, 2003 (DMETS)
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Yes, listed in approval letter
• Documentation of discussions and/or agreements relating to post-marketing commitments	No
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	April 29, 1994
• Pre-NDA meeting (indicate date)	December 12, 1997
• Pre-Approval Safety Conference (indicate date; approvals only)	ODS was involved with all label discussions and provided input, but no formal safety conference took place
• Other	
❖ Advisory Committee Meeting	

• Date of Meeting	December 9, 2003
• 48-hour alert	Not Applicable
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	Volume 68, Number 98 Wednesday May 21, 2003
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	A. Jacobs: January 27, 2006 N. Stockbridge: January 22, 2006 and September 29, 2003 R. Temple: January 27, 2006 and November 19, 2003 A. DeFelice: February 6, 2006 and October 17, 2003
❖ Clinical review(s) *(indicate date for each review)*	January 24, 2006 December 8, 20, and 21, 2005 Medical/Statistical: November 30, 2005 September 2, 12, and 25, 2003 Efficacy: August 28, 2003 Safety: July 30, 2003 and September 26, 2003
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	Not Applicable
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	April 28, 2003
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Waived: August 31, 2001
❖ Statistical review(s) *(indicate date for each review)*	August 28, 2003
❖ Biopharmaceutical review(s) *(indicate date for each review)*	November 28, 2005 October 8, 2003 September 15, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	Not Applicable
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	February 8, 2006 and August 28, 2003
• Bioequivalence studies	Not Applicable
❖ CMC review(s) *(indicate date for each review)*	January 11, 2006 December 6, 2005 October 10, 2003 September 16, 2003
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	September 16, 2003
• Review & FONSI *(indicate date of review)*	Not Applicable
• Review & Environmental Impact Statement *(indicate date of each review)*	September 16, 2003
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	Not Applicable
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable (X) Pending ( ) Withhold recommendation

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

/s/

Margaret Pease-Fye
2/13/2006 10:44:36 AM

18 USER FEE COVER SHEET

A small business waiver of the application fee for NDA 21-526 was granted by a letter from FDA on 27 September 2002. A completed Form FDA 3397, Prescription Drug User Fee Cover Sheet, signed on 19 December 2002, and a copy of the FDA correspondence confirming the waiver were included in the original NDA submission dated 27 December 2002 (Item 18, Vol 1, p 42).

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 27 2002

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

RE: CV Therapeutics, Inc., Small Business Waiver Request 2003.008 for Ranexa (ranolazine)

Dear Ms. Karp:

This responds to your August 7, 2002, letter requesting a waiver of the human drug application fee for the new drug application (NDA 21-526) for Ranexa (ranolazine) under the small business waiver provision of section 736(d)(1)(E)[1] of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2003.008). For the reasons described below, the Food and Drug Administration (FDA) grants the request from CV Therapeutics, Inc. (CVT), for a small business waiver of the application fee for NDA 21-526 for Ranexa (ranolazine).

According to your waiver request, CVT is a small business with — employees and no products in interstate commerce in the United States or in foreign countries. You add that CVT has no affiliates and no previous market applications. The waiver for NDA 21-526 for Ranexa (ranolazine) will be the first market application for CVT or its affiliates. You plan to submit this new NDA by the end of calendar year 2002.

Under the Act, a waiver of the application fee shall be granted to a small business for the first human drug application that a small business or its affiliate[2] submits to the FDA for review. The small business waiver provision entitles a qualified small business to a waiver when the business meets the following criteria: (1) a business must employ fewer than 500 persons, including employees of its affiliates, and (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

FDA's decision to grant CVT's request for a small business waiver for NDA 21-526 for Ranexa (ranolazine) is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its letter dated September 23, 2002, that CVT has fewer than 500 employees and no affiliates. Second, according to FDA records, the marketing application for Ranexa will be the first human drug application, within the meaning of the Act, to be submitted to FDA by CVT or its affiliates. Consequently, your request for a small business waiver of the

[1] 21 U.S.C. 379h(d)(1)(E).
[2] "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

application fee for NDA 21-526 for Ranexa (ranolazine) is granted provided FDA receives the marketing application for Ranexa (ranolazine) no later than September 23, 2003, 1 year after the effective date of the size determination made by SBA.

FDA records show that CVT's NDA 21-526 has not yet been submitted to FDA. Please include a copy of this letter with your application when it is submitted. If FDA refuses to file the application or CVT withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, CVT should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether it continues to qualify for a waiver.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

RHPM Overview of NDA 21-526
Ranexa (ranolazine) 500mg Extended-Release Tablets
January 27, 2005

Sponsor:	C.V. Therapeutics
Type:	1S
Resubmission Receipt Date:	July 27, 2005
User Fee Goal Date:	January 27, 2006

Background

Ranexa (ranolazine) ER was developed for treatment of chronic angina in patients with severe coronary artery disease in patients, in whom other anti-anginals are inadequate or not tolerated. The Office of Drug Evaluation I sent an Approvable letter to CV Therapeutics on October 30, 2003 outlining the following deficiencies:

- Dose was not adequately characterized sufficiently to provide labeling instructions. Additional dose-response information will be necessary.
- The Agency had the following three safety concerns that need to be addressed:

    1. Potential testicular toxicity
    2. Delayed cardiac repolarization, manifest clinically as prolongation of the QT interval
    3. Inadequate safety exposure

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

A Cardiovascular and Renal Drugs Advisory Committee Meeting was held on December 9, 2003 where a minority of the Committee felt that there were adequate data to permit approval of ranolazine for use in either an unrestricted or a restricted population, but the majority of the Committee felt that further information was needed to address the following:

- effectiveness in the indicated population
- durability of effectiveness
- instructions for use in various subgroups
- characterization of treatment-related syncope

CV Therapeutics submitted two Special Protocol Assessment (SPA) requests to meet these deficiencies under their IND (43,735). The first, submitted March 4, 2003 (S-223) was for the protocol entitled, "A Double-Blind, Randomized, Placebo-Controlled, Parallel Group Study of Ranolazine ER at a Dose of 1000 mg Twice a Day in Patients with Chronic Angina Who Remain Symptomatic Despite Concomitant Treatment with Amlodipine 10 mg Once a Day." This protocol is also called CVT 3037.

The second SPA submitted under the IND was for the protocol entitled, "A Randomized, Double-blind, Parallel-group, Placebo-controlled, Multinational, Clinical Trial to Evaluate the Efficacy and Safety of Ranolazine versus Placebo in Patients with non-ST segment Elevation Acute Coronary Syndromes." This protocol is also referred to as CVT 3036 and was submitted to the Division on May 7, 2004 (S-232).

Once the NDA was resubmitted, an internal meeting was held on September 15, 2005 where it was determined that:

- The issues raised in the approvable letter were adequately addressed in the resubmission
- The issues concerning tumor promotion do not need to be addressed at this time for the indication in a refractory population
- The acknowledgement letter should explain that CV Therapeutics must address concerns regarding the finding of the study in the APC (min/+) mouse model to pursue an indication in the general population

Correspondence and meetings regarding the development of Ranexa and regulatory review process beginning with the action letter include:

1. October 30, 2003 Approvable letter
2. December 9, 2003 Cardio-Renal Advisory Committee Meeting
3. February 6, 2004 Meeting to discuss trial design strategies
4. April 16, 2004 Meeting to discuss TIMI study design issues
5. April 23, 2004 Letter conveying conclusion that the "characterization of the dose-response relationship for Ranexa would not be necessary if CV Therapeutics were to find compelling evidence that Ranexa has beneficial effects on cardiovascular effect in the TIMI trial, or if one dose has demonstrated efficacy in patients with resistant angina (study CVT 3037). However, if CV Therapeutics is interested in a symptomatic claim for angina, such data are necessary but those data need not be obtained from study CVT 3037."
6. October 27, 2004 Teleconference to discuss details of proposed study design for CVT 3023 (dose-escalation study to characterize higher doses)
7. November 22, 2004 Meeting to discuss amendment to the NDA based on SPA response
8. April 27, 2005 Teleconference to discuss recommended modifications to CVT 3023 study design
9. May 4, 2005 Information request for response to Cancer Letters article
10. July 26, 2005 Acknowledgement letter for a Class 2 resubmission
11. November 28, 2005 Memo to File noting comments from DDMAC and DMETS for trade name review were sent to the sponsor via e-mail
12. December 22, 2005 Letter from DDMAC with additional comments

Medical Review

In her review dated December 8, 2005, Dr. Targum recommended that an approvable action be taken for ranolazine. She made the following recommendations:

- The lingering question of whether ranolazine is a tumor promoter needs to be addressed. If ranolazine is approved, with the other safety issue, ranolazine's concentration-related QT prolongation, and the availability of other treatments without effects on repolarization, ranolazine should not be a first-line drug for angina.
- If ranolazine were to be approved, Dr. Targum recommended a "black box" warning regarding QT prolongation. She opines that this drug should not be directly marketed to consumers.
- If ranolazine were to be approved, instructions for use will need to take into account ranolazine's interactions with verapamil and diltiazem, as well as the inter-subject variability.
- The smaller treatment effect in women and safety profile in the elderly should receive mention in labeling.

Support for efficacy was based on three double-blind, placebo-controlled studies (CVT 3031, CVT 3033, CVT 3037) which supported a claim of efficacy. Two of these studies (CVT 3031 and CVT 3033) were part of the original submission and review.

In the original submission (2003), CVT 3033 and CVT 3031 supported a treatment effect of increased ETT duration (more convincing at peak); however, given the known ranolazine effect on repolarization, the Agency recommended that data be provided demonstrating that ranolazine has benefits which offset the concern arising from effects on the QT interval. One way is to show efficacy in a population not adequately treated with maximally tolerated or labeled doses of an approved anti-anginal. CVT 3037, a study of ranolazine in an angina population with symptoms despite amlodipine 10 mg daily, was reviewed in this submission and supports the reduction in angina attack rate and nitroglycerin consumption seen in CVT 3033.

The medical review concludes, based on the results of CVT 3033, CVT 3031 and CVT 3037, that ranolazine demonstrated a modest effect on symptoms and exercise duration; to date there are no data to show effects on cardiovascular outcomes (*e.g.,* MI, death). In the resubmission, a treatment effect is demonstrated in a patient population receiving amlodipine and (about half of the study population) nitrates. A safety update from the sponsor, dated November 21, 2005, was reviewed separately.

Outstanding issues with regard to ranolazine include:

1. resolution of the question of tumor promotion raised in the pharmacology/toxicology review (discussed below)
2. establishment of ranolazine's effect on cardiac repolarization
3. exploration of ranolazine effects in females
4. further exploration of dose-response, including evaluation of doses below 500 mg bid
5. further understanding of the mechanism of action of ranolazine.

The question of tumor promotion, raised by Dr. Hausner, is based on a publication by Suckow et. al. Standard carcinogenicity testing was negative and there does not appear to be evidence that ranolazine causes tumors.

Dr. Targum believes there is some biological plausibility that ranolazine might facilitate tumor growth. If ranolazine leads to more efficient energy production in hypoxic myocardial tissue, an "unintended consequence" of promoting might be a more efficient energy production in hypoxic tumors. There is also some uncertainty; the Suckow paper involved a model in one mouse and has not been reproduced in other species or other systems.

CV Therapeutics did not attempt to replicate the published study (or show that the results are not reproducible). Suckow et. al. did not study a broad range of drugs in this particular model. Dr. Hausner analyzed the clinical program for incidences of cancer; however, lack of a signal in the clinical program may not be meaningful as the long-term ranolazine exposure may not have included enough cancer patients and did not include a background rate for comparison.

The regulatory options include:

1. approval (pending appropriate labeling) with safety information (including drug effects on repolarization and the unresolved question of tumor promotion) communicated to patients and health care providers
2. an approvable action, asking the sponsor to convince the Agency that results from the Suckow article are not reproducible or not of concern. Dr. Hausner chose the latter option.

The Agency has stated that further dose exploration is not needed if efficacy were demonstrated in CVT 3037 (*e.g.*, a "resistant population" or population with angina despite treatment).

Recommendation on Phase 4 Studies and/or Risk Management Steps

Risk Management Activity: There have been no agreed-upon risk management activities between the Agency and the sponsor; however, the sponsor should consider a risk management approach regarding appropriate ECG monitoring for repolarization changes and QT prolongation.

Required Phase 4 Commitments: There are two required phase 4 commitments associated with this review or submission:

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

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

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

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

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

Other Phase 4 Requests:

1. If ranolazine were to be approved, the sponsor should adequately explore and address the question of tumor promotion raised in the Suckow article.
2. The sponsor should explore effectiveness in women in an adequate, well-controlled study in females with coronary artery disease.
3. The sponsor should be encouraged to explore tolerability of ranolazine in the elderly population.
4. The sponsor should explore dose-response, including evaluation of efficacy of lower doses of ranolazine ER.

Joint Medical and Statistical Review of CVT 3037

Drs. Targum and Freidlin described the pivotal trial CVT 3037 in their combined review of November 30, 2005:

- The trial was a double-blind, placebo-controlled parallel-group study evaluating the effect of ranolazine 1000 mg bid on average weekly angina attacks (via patient diary).
- Due to the presence of outliers, the study analysis was changed to a non-parametric analysis (changes reviewed by the Agency). The study met its primary endpoint.
- Limitations of this study included:

- Patient-reporting: Unless the diary reporting is contemporaneous with the angina attack, reporting may be subject to differences in memory and recollection of events. Patients may also differ in their perceptions of angina attacks (some may interpret every pain as angina, whether or not cardiac in origin).
- Activity: Since level of activity is not controlled or tested in this trial, the weekly rate of angina attacks may be subject to varying levels of activity (as opposed to drug effect).
- Seattle Angina Questionnaire: While originally listed as a secondary endpoint, the SAQ has not been validated in the study population and will not be used by these reviewers in regulatory decision-making.

Since the study was blinded and placebo-controlled, one would hope that the issues raised above will occur equally in both groups.

- No significant treatment effect was seen in the female subgroup. The sponsor has noted that the female subgroup has a smaller sample size. While the sample size is smaller for the female subgroup, it is worth noting that the effect size for the primary endpoint is also smaller in females compared to the effect size in males.
- A shift in creatinine was seen in the ranolazine group; however, no safety signal was seen in this study with regard to treatment-emergent or serious renal AE.
- The following treatment-emergent AE were increased in the ranolazine group:

  constipation
  nausea
  peripheral edema
  dizziness

  Slight increases were seen with regard to: dry mouth, dyspepsia, asthenia, and abdominal pain. No safety signals were seen with respect to discontinuations due to AE or serious/fatal AE.
- Higher rates of constipation and peripheral edema were reported in the elderly.

Pharmacology Review

In her review dated October 31, 2005, Dr. Hausner briefly summarizes that the sponsor is proposing ranolazine as the first in a new mechanistic class. The two studies reviewed were cited in the sponsor's annotated labeling to support the proposed mechanism of action. For reasons cited in her reviews, she believes the studies themselves are suboptimal; if the argument that ranolazine in the μM range does have effects on the INa is accepted, the following questions should be considered:

1. What is the *in vivo* biological significance of this effect?
2. How many other drugs can modulate this channel?
3. What distinguishes this from the Na+ channel blockers used as anti-arrhythmics, *e.g.* encainide (no longer available) and flecainide?

She notes that the sponsor tries to draw a theoretical bridge when they stated:

> In ischemic conditions the late sodium current is increased, leading to intracellular sodium overload. Sodium overload leads to calcium overload as a result of either a decrease in the efflux of calcium ions via the forward mode of the Na-Ca exchanger (NCX) or an increase in the efflux of calcium ions via the reverse mode of the NCX, or both. Calcium overload during the ischemia causes slowing of the left ventricular relaxation and an increase of left ventricular diastolic stiffness. Ranolazine by inhibiting this pathologically-enhanced late sodium current, reduces intracellular sodium and calcium loading of ventricular muscle cells, and thereby improves ionic homeostasis. The reduction in cellular calcium overload is expected to reduce myocardial stiffness, oxygen consumption and ATP utilization.

In a further discussion of the relevance of the late sodium channels, the sponsor cites that:

> During ischemia, sodium influx via late INa appears to be a major contributor to the rise of [Na+]i.53 Sodium channel blockers (e.g. tetrodotoxin, lidocaine) have been shown to reduce the rise in [Na+]i in rat ventricular myocytes and isolated hearts during hypoxia and ischemia respectively. This reduction in the rise concentration ([Ca2+]i) and improvement in contractile function.

The sponsor goes on to state that, in addition to the peak and late sodium currents, the sodium/hydrogen exchanger and the sodium calcium exchanger are two important pathways responsible for the regulation of sodium entry into cells, contributing to maintenance of cardiac intracellular sodium and calcium homeostasis. There is no clear statement of mechanism but the implication is that complex electrophysiological interactions make up the overall mechanism.

Although Dr. Hausner did not review all of the submitted studies, all studies were examined for use of comparator compounds, the most appropriate comparators appearing to be Class I anti-arrhythmics, such as encainide, flecainide or quinidine. The sponsor did not use this kind of comparison.

Dr. Hausner concluded that approvability depends upon the clinically demonstrated risk:benefit ratio. She also made the following comments on labeling:

> **DESCRIPTION** section should read [
>
>]
>
> **CLINICAL PHARMACOLOGY,** ***Mechanism of action*** section should read "The mechanism of action is uncertain." The next 3 paragraphs should be removed.

Based on conversations with the Pharmacology/Toxicology Coordinating Committee and consultation from the National Toxicology Program, Dr. Hausner made the following additional recommendations on December 15, 2005:

> A. Approvability: that ranolazine be approvable contingent upon the sponsor satisfactorily addressing the issue of cancer promotion.
>
> B. Non-clinical studies: Studies need to be performed that will address the issues raised by the 2-year rodent carcinogenicity studies and the APC+/-min mouse study.
>
> C. Labeling: Should ranolazine be approved without resolution of this matter, a black box warning should be included to let potential users know of the possibility of promotion of pre-cancerous lesions or existing cancerous lesions.

Biopharmaceutical Review

In his review dated November 28, 2005, Dr. Hinderling stated that the Office of Clinical Pharmacology and Biopharmaceutics had reviewed the Type 2 resubmission of NDA 21-526 and found the clinical pharmacology and biopharmaceutics sections acceptable provided the labeling comments are adequately addressed.

Issues raised by Dr. Hinderling include:

1. marketing ranolazine in one strength only, the non-scored 500 mg tablet, limiting the capability of adjusting the dose
2. deletion of the 12 hour value in the dissolution specifications
3. failure of study 301-16 to definitively delineate the mechanism responsible for serum creatinine elevation in the presence of ranolazine.

Chemistry Review
Both in his December 16, 2005 review, and in his January 11, 2004 review, Dr. Raman recommended Approval for this application. An overall acceptable recommendation was received from the Office of Compliance regarding manufacturing facilities on August 16, 2005. Updated stability data up to [redacted] on drug substance and the drug product was provided and was satisfactory. In response to DMETS comments, dated 11/23/05, on proposed labeling for ranolazine, the applicant submitted revised container labels and labeling for Ranexa, in accordance with DMETS recommendations.

Dr. Raman had the following comments regarding retest date for the drug substance, expiration date and dissolution specification for the drug product:

- A retest date of [redacted] 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 [redacted] rpm , 0.1N HCl, [redacted] ml, vessel temperature 37°C ± 0.5°C, sampling time and acceptance criteria of 0.5 hr [redacted] 4 hr [redacted] 12 hr [redacted] and 20 hr (NLT [redacted]

Division of Scientific Investigations
An investigation of sites in Russia was completed on January 27, 2005. No Form 483 was filed.

Pediatrics
The Sponsor requested and was granted a waiver on August 31, 2001 for pediatric studies pursuant to the Pediatric Rule.

Labeling
The Sponsor submitted annotated proposed labeling, as well as carton and container labeling in the re-submission. The labeling was reviewed by DMETS on November 21, 2005 and DDMAC on December 22, 2005. DDRE also provided unofficial comments on December 22, 2005.

Advisory Committee Meeting
An Advisory Committee meeting was held on December 9, 2003. Transcripts of those proceedings are included in this action package.

CSO Summary
Per Dr. Stockbridge's instructions, an approval letter will be drafted for Dr. Temple's signature.

Meg Pease-Fye, M.S.
Regulatory Health Project Manager
January 27, 2005

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/s/

Margaret Pease-Fye
2/1/2006 12:10:05 PM
CSO

RHPM Overview of NDA 21-526
Ranexa (ranolazine) 375mg and 500mg tablets
September, 2003

Sponsor:	C.V. Therapeutics
Type:	1S
Submission Date:	December 27, 2002
Receipt Date:	December 30, 2002
User Fee Goal Date:	October 30, 2003

Background

Ranexa (ranolazine) SR is being developed for treatment of chronic angina in patients with severe coronary artery disease in whom other anti-anginals are inadequate or not tolerated. The Division sent a Discipline Review letter to the Sponsor on July 17, 2003 identifying specific concerns. The Sponsor was given the opportunity to present before the Cardio-Renal Advisory Committee but believed they would not have time to both prepare for the committee and respond to the reviewer's issues. A teleconference (July 18, 2003) was held to assist the Sponsor with clarification of review issues. The Sponsor sent in a submission outlining their intent to submit additional materials they believe may constitute a major amendment that would push back the due date by three months and provide an opportunity for the drug to go before the December Advisory Committee. These materials were received September 15, 2003. On October 1, 2003 a teleconference was held to alert CV Therapeutics that the data in the amendment was found not to make a material contribution to the issues raised by those reviewers and did not meet the requirements to extend the goal date. At this teleconference, the Division invited CV Therapeutics to present before the December Advisory Committee.

Previous correspondence and meetings regarding the development of Ranexa and regulatory review process include:

1. July 29, 2000 guidance meeting
2. February 27, 2001 teleconference to discuss proposed and on-going pre-clinical and clinical studies
3. December 20, 2001 pre-NDA teleconference
4. August 13, 2002 guidance meeting
5. October 10, 2002 pre-NDA meeting
6. February 25, 2003 filing meeting
7. July 7, 2003 teleconference to discuss the potential of Ranexa to go before an Advisory Committee in September, 2003
8. July 18, 2003 teleconference to discuss reviewer comments
9. July 31, 2003 teleconference to clarify Pharmacology issues
10. August 1, 2003 teleconference to discuss September Advisory Committee meeting
11. August 7, 2003 teleconference to discuss Clinical Pharmacology and Biopharmaceutics issues
12. August 11, 2003 teleconference to discuss Biostatistics issues
13. September 3, 2003 teleconference to further discuss Biostatistics issues
14. October 1, 2003 teleconference discussing the data in the amendment submitted on September 15, 2003 and to invite CVT to go before the December Advisory Committee.

Medical Review-Safety
In her review dated July 30, 2003, Dr. Gordon noted evidence that ranolazine increases the QT interval on ECG and changes the morphology of the notched T wave. These increases appear to be dose-related and may be affected by other drugs and conditions. Specifically, the following may increase the plasma concentration of ranolazine:

- CYP3A4 inhibitors (eg. Ketoconizole)
- Diltiazem
- Simvastatin
- Hepatic and renal impairment

Dr. Gordon notes that the use of ranolazine poses a serious risk. Dr. Gordon made no recommendation as to this application's approvability.

In terms of the September 15, 2003 amendment, she notes that the Sponsor did not submit any information that changed her assessment of risk associated with ranolazine's effect on the QT interval.

Medical Review-Efficacy and Statistical Review
Drs. Targum and Freidlin opined in their combined review of August 28, 2003:

- There are mixed data in the pivotal studies. A treatment effect is shown at peak; however, only marginal effects are shown at trough. The crossover analysis was difficult to interpret; a statistically significant effect at trough cannot be concluded, although a statistically significant treatment effect at trough for the sustained release formulation is seen after 2 weeks of treatment. Also, there is insufficient evidence to conclude that ranolazine SR, when given bid, is effective throughout the inter-dosing interval. Therefore, the concern remains that the duration of effect, and consequent dosing schedule, is uncertain.

- There appears to be no greater treatment effect with increase in dose from 750 to 1000 mg bid.

- Although ranolazine appears to exhibit an anti-anginal effect, as measured by exercise testing, at the time of peak levels (4 hours after dosing), there are no studies demonstrating superiority of ranolazine over other antianginal medications. The proposed labeling projected an indication for "treatment of chronic angina in patients with severe coronary artery disease, and should be reserved for use in patients in whom other anti-anginals are inadequate or not tolerated." Neither pivotal trial studied this group or predefined "inadequate or not tolerated." The data are insufficient to demonstrate whether ranolazine has a beneficial effect in symptomatic patients on maximal anti-anginal therapy.

- There are insufficient data, whether in the pivotal trials or Integrated Summary of Efficacy, to show efficacy of the primary endpoint in people with low blood pressure or reactive airway disease, as mentioned in the labeling. Additionally, in the gender subgroup analysis, the treatment effect at peak, in females, showed an unfavorable trend. The study population was about 98% Caucasian and no other race groups were well studied. There are insufficient data to demonstrate efficacy of ranolazine in non-Caucasian subgroups.

In terms of this applications approvability, Drs. Targum and Freidlin made the following recommendations:

1. The Sponsor can perform an appropriately sized outcomes trial showing an improved survival on ranolazine vs. placebo. OR

2. The Sponsor should perform an additional study evaluating benefit of ranolazine in a refractory angina population. As an example, the Sponsor can show a benefit of ranolazine vs. placebo in a population of symptomatic patients on maximal medical therapy who are not candidates for PCI or surgery (either due to co-morbidity or coronary anatomy).

3. The Sponsor would also need to clarify appropriate dosing and dosing interval. Since the crossover study design presented interpretability problems for the Agency, the Sponsor is encouraged to perform another parallel-group study supporting ranolazine's efficacy at trough.

4. In addition, the Sponsor should be asked to evaluate efficacy of ranolazine in women; the Sponsor could, potentially, incorporate some type of gender evaluation in a study of refractory patients.

Recommendation on Phase 4 Studies and/or Risk Management Steps
Drs. Targum and Freidlin stated that if ranolazine were to be approved, they would recommended some risk management steps be undertaken to minimize the risk of *torsade de pointes*. These risk management steps can include labeling recommendations and education programs for physicians, patients, and pharmacies.

Dr. Targum also addressed the financial disclosure on page 19 of this review.

In terms of the amendment received on September 15, 2003, additional efficacy subgroup analyses from studies CVT 3031 and CVT 3033 were submitted. Treadmill exercise data were analyzed in:

1. An aggregate of patients with either reactive airway disease, CHF, diabetes or low BP, slow heart rate, or PR prolongation

2. Patients with a prior myocardial infarction (MI)

3. Patients who have undergone a revascularization procedure.

In addition, analyses of patient reported angina frequency and nitroglycerin use were conducted for each of the above subgroups. Given the difficulties in interpreting the primary efficacy endpoint in CVT 3031, it was not clear how to interpret post-hoc subgroup analyses from CVT 3031. The post-hoc subgroup analyses from CVT 3033 were also reviewed and Dr. Targum concluded that these analyses did not add to or alter the conclusions of the efficacy review

Secondary Medical Review
In his memo dated September 29, 2003, Dr. Stockbridge outlines the rationale for the approvability recommendation for the use of ranolazine. He summarized the ambiguous findings concerning the drug's mechanism of action as well as the results of the clinical studies. He concluded that, the "restriction of use to a population refractory to usual treatments is the only sensible option."

Pharmacology Review

In her review dated September 3, 2003, Dr. Hausner noted that in terms of animal pharmacology and toxicology, ranolazine appears to interact with cardiac ion channels. Approximately seven of the known major metabolites were shown to interact with cardiac ion channels. The cardiovascular safety study showed that cumulatively increasing doses of ranolazine caused a deterioration in cardiac function displayed as decreased cardiac output, decreased contractile force and decreased left ventricular systolic pressure. Left ventricular minute work was also decreased while total peripheral resistance was increased. ECG data was not provided.

She noted sedation in several of the neurologic safety pharmacology assessments as well as general toxicology studies. Neurologic deficits were observed at doses where sedation was not apparent.

Dr. Hausner further concluded that, in general toxicology studies, adrenal weight was increased in both rats and dogs. Where pathology was reported, histopathologic findings included diffuse vacuolation and/or cytoplasmic foaminess of the zona fasciculata. Special toxicology studies showed both acute and chronic effects of ranolazine on the hypothalamicpituitary-adrenal (HPA) axis. Both *in vitro* and *in vivo* studies showed that ranolazine treatment caused a decrease in the release of adrenal steroid in the basal state, after ACTH stimulation, after a defined stressor and in the presence of precursors.

Ranolazine and/or one of its metabolites bind to retinal pigmented epithelium with a half life of 8 days, most likely due to melanin binding. Accumulation in the retina and long term effects, if any, upon vision, are unknown.

Dr. Hausner also concluded that approvability depends upon the clinically demonstrated risk:benefit ratio. She also made comments on labeling.

In an additional memo to the file concerning the amendment received on September 15, 2003, she states that the material submitted did not significantly contribute to elucidation of histopathological questions and that it does not materially change the pre-clinical characterization of ranolazine

In a separate review dated September 4, 2003, Dr. Koerner concluded that ranolazine's non-clinical electrophysiological effects are generally consistent with QT interval prolongation observed in clinical trials. He notes, however, the Sponsor provided information arguing against proarrhythmic properties of ranolazine.

Further, he noted that, in theory, torsade de pointes with QT prolonging drugs arises from increased transmural dispersion of repolarization and triggered activity (early afterdepolarizations) rather than from QT interval prolongation, per se. The elegant models of Antzelevitch argue that findings in isolated canine ventricular strips and wedge preparations, in particular action potential lengthening and early afterdepolarizations in M-cells, transmural dispersion of repolarization, and induction of torsade-like arrhythmias in vitro can predict proarrhythmic potential of a drug. Theory is supported in part utilizing data from positive control drugs such as amiodarone, cisapride, d-sotalol, erythromycin, quinidine and terfenadine.

Dr. Koerner also concludes that, while findings with ranolazine are primarily negative in the isolated canine ventricular wedge preparation, ranolazine increases M-cell action potential duration and transmural dispersion of repolarization under conditions of hypokalemia. He believes these findings are consistent with its ability to inhibit repolarizing currents, IKr and IKs, at concentrations similar to those required for its proposed mechanism of action. Moreover, proarrhythmic potential was not adequately

evaluated since ranolazine was not tested under conditions necessary to capture cisapride-induced arrhythmias in this model. Additionally, *in vivo* evaluation for proarrhythmia was not comprehensive.

He raised additional regulatory concerns reflecting the complex nature of any proarrhythmia model, lack of evaluation of metabolites in this in vitro model, and adequacy of testing for proarrhythmia, utilizing known risk factors for clinical arrhythmias, e.g. female gender, different pacing modalities (pause, acceleration), adrenergic influences, and heart failure.

In conclusion, Dr. Koerner states that, for these reasons, study results provided by the Sponsor cannot preclude the risk of proarrhythmia with ranolazine.

Secondary Pharmacology Review
In his memo dated October 17, 2003, Dr. DeFelice concluded that in a study of male rat fertility, ranolazine impaired fertility at the lethal HD, which may have reflected no or reduced sperm counts in four rats. He also noted no other chronic rat or dog toxicity study identified testicular toxicity, although, he agrees with Dr Hausner, that the histopathology tables were not forthcoming in relevant toxicity studies. Further, regarding teratogenicity, he stated that there was none, even at maternocidal dosages, and regarding embryotoxicity, there were reductions in implantation indices but not when corrected for increases in ovulation. There were decrements in fetal weight and neonatal developmental delays, especially at the HD.

Dr. DeFelice further concluded that the evaluation and identification of selective reproductive toxicity is confounded by maternal and paternal toxicity that occurs at or within a few-fold of human AUC exposures. He states that determining extent to which any reproductive toxicity is selective is further compromised by an excessive interval between mid and high dosages which precludes the determination of toxicity thresholds.

Biopharmaceutical Review
In his review dated September 15, 2003, Dr. Hinderling concluded that the clinical pharmacology and biopharmaceutics sections are acceptable provided that 30 labeling comments are adequately addressed. In addition, the Division of Clinical Pharmacology and Biopharmaceutics has offered the following recommendations to the Sponsor:

1. As a Phase 4 commitment perform a drug interaction study in healthy volunteers of both genders investigating the potential of ranolazine to inhibit the metabolism of a probe substrate mainly metabolized by CYP 2D6.

2. Change the proposed dissolution specifications according to FDA recommendations (as noted in their review).

Dr. Hinderling made no additional comments concerning the amendment of September 15, 2003.

Chemistry Review
In his September 16, 2003 review, Dr. Chidambaram concluded that this application is approvable. He believed that he received satisfactory responses concerning the deficiencies in chemistry, manufacturing and controls, 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.

Dr. Chidambaram also addressed the environmental assessment and categorical exclusion on page 77 in his review and found them to be acceptable.

After reviewing the September 15 submission, Dr. Chidambaram concluded that the application be recommended for APPROVAL from the perspective of chemistry, manufacturing and controls. He received satisfactory responses to the deficiencies concerning drug substance and drug product previously identified and conveyed to the applicant. An acceptable recommendation was received from the Office of Compliance regarding manufacturing facilities on October 6, 2003, and is attached to his second review. A retest date of [redacted] for the drug substance and an expiration period of [redacted] for the drug product will be granted based on the stability data provided.

Division of Scientific Investigations
In a memo dated August 21, 2003 DSI found the data for both inspected sites verifiable and further, found no issues that would bring the validity of the data into question at either of the two sites.

Pediatrics
The Sponsor requested and was granted a waiver on August 31, 2001 for pediatric studies pursuant to the Pediatric Rule.

Labeling
The Sponsor submitted annotated proposed labeling, as well as carton and container labeling was in the original submission and was reviewed by DMETS on June 6, 2003. On September 15, 2003, revised labeling was submitted. DDMAC has not submitted comments for this cycle.

Advisory Committee Meeting
No meeting was held.

CSO Summary
Per Dr. Throckmorton's instructions, an approvable letter will be drafted for Dr. Temple's signature.

Meg Pease-Fye, RHPM
October 23, 2003

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/s/

Margaret Pease-Fye
12/20/2005 04:35:03 PM
CSO

This PM Overview was inadvertantly not DFS'ed after the first cylce PDUFA date.

49 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

34 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(4) Draft Labeling

3 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(4) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW ISSUES IDENTIFIED

NDA 21-526

3/14/03

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

Dear Ms. Karp:

Please refer to your December 30, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ranexa (ranolazine) extended release 375 and 500 mg Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 28, 2003 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. The proposed [ ] shelf life does not appear to be supported by your submitted [ ] stability data.

2. Your fertility and teratogenicity data do not appear to be adequate because of disease and mortality in these studies.

3. Data submitted do not appear to be adequate to characterize binding of ranolazine to non-target receptors (e.g. opioids).

4. The validation reports for the bioanalytical methods are not available for all the Clinical Pharmacology studies.

5. An individual report describing methods and results of the comparative dissolution testing of the commercial and service forms of the 375 and 500 mg tablets was not submitted. Details on the data points used for the computation of the reported f2 values were not provided.

6. Adequate data do not appear to have been submitted to characterize pharmacological and clinical effects of the two enantiomers of ranolazine.

7. Adequate data do not appear to have been submitted to characterize pharmacological and clinical effects of the metabolites of ranolazine.

8. A detailed description of the methods used to measure the QT interval was not provided in the clinical reports submitted (as requested by fax of March 5).

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.

In addition to addressing the issues cited above, we also request that you submit the following information:

1. Identify studies supporting the assertion made in the proposed labeling "Mechanism of Action" section , [ ] (as requested in telephone conversation 2/25/03).

2. Justify your identification of the effects on fatty acid metabolism as the specific mechanism of action (as requested in telephone conversation 2/25/03).

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 Meg Pease-Fye, Regulatory Project Manager, at (301) 594-5312.

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
3/14/03 02:09:42 PM
For Douglas Throckmorton

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-526

2/25/03

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

Dear Ms. Karp:

We have received your new drug application (NDA) 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, and 500 mg

Date of Submission: February 19, 2003

Date of Receipt: February 20, 2002

We concur with your plans as outlined in the submission referred to as the Formal Plan for Four-Month Safety Update.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products
Attention: Division Document Room, HFD-110
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Document Room
1451 Rockville Pike, 5th FLoor
Rockville, Maryland 20852

If you have any questions, call Meg Pease-Fye, Regulatory Project Manager, at (301) 594-5312.

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton,
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doug Throckmorton
2/25/03 09:49:07 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-526

INFORMATION REQUEST LETTER

2/26/03

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

Dear Ms. Karp:

Please refer to your December 27, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ranexa (ranolazine) extended release Tablets, and 500mg.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please define how the QT intervals were measured in the ranolazine clinical trials (including pharmacology trials) including what lead was used, definition of end of T wave criteria, how many were read manually, were readers blinded, the number of beats considered, and the acceptance /exclusion criteria.

If you have any questions, call Meg Pease-Fye, Regulatory Health Project Manager, at (301) 594-5312.

Sincerely,

Norman Stockbridge, M.D., Ph.D.
Deputy Division Director,
Division of Cardio-Renal Drug Products, HFD-110
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
2/20/03 03:31:20 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-526

1/13/03

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

Dear Ms. Karp:

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

Name of Drug Product: Ranexa (ranolazine) 375/500 mg Tablets

Review Priority Classification: Standard

Date of Application: December 27, 2002

Date of Receipt: December 30, 2002

Our Reference Number: NDA 21-526

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 February 28, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 30, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division ofCardio-Renal Drug Products, HFD-110
Attention: Document Room 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

Zelda McDonald
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Zelda McDonald
1/13/03 03:16:22 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-526

DISCIPLINE REVIEW LETTER

7/17/03

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

Dear Ms. Karp:

Please refer to your December 27, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ranolazine 375 and 500 mg Tablets.

We also refer to your submissions dated January 29, February 12, 18, 19, 25, 27 and 28, March 7, 18, 21, and 24, April 2, 3, 4, 8, 11, 15, 28, 29, and 30, May 2, 6, 20, and 23, June 5, 6, 17, and 25 and July 1, 2003.

During review of the Clinical, Statistical, Chemistry, Manufacturing and Controls, Pharmacology and Toxicology, and Biopharmaceutics sections of your submission, the primary reviewers have identified, to date, the following potential review issues:

Safety issues

1) There is a substantial concentration-related increase in mean QT/QTc interval (10 msec or more). We need a list of drugs (e.g., ketoconazole) and disease states (e.g. hepatic impairment) that would increase the safety concern with ranolazine.

2) There is a concentration-related increase in the incidence rate of notched T waves. Are there data showing that this effect increases or decreases the safety of ranolazine?

Efficacy Issues

1) The pivotal studies, including 3031 (first period) and 3033, show a treatment effect at peak; only one study (3033) shows a marginally significant effect at trough (see Statistical Issues). It is therefore a concern that the duration of effect, and consequent dosing schedule, is uncertain.

2) In the proposed labeling submitted by the sponsor, the proposed indication is for "treatment of chronic angina in patients with severe coronary artery disease, and should be reserved for use in patients in whom other anti-anginals are inadequate or not tolerated." Neither pivotal

trial specifically studied this group, nor were the terms, "inadequate or not tolerated" pre-defined.

Clinical Pharmacology issues

1a) The ETT efficacy of ranolazine at trough following administration of 500 mg to 1500 mg bid was not consistently demonstrated in the pivotal trials. Hence, the time duration of ranolazine's ETT efficacy is not defined and the adequacy of the bid regimen is questionable.

1b) The respective relationships between the ranolazine plasma concentrations and the effect on ETT in males and females are characterized by significantly different slopes. In women, the slope is about 33% of the slope in males. This finding suggests that the magnitude and, consequently, the time duration of the ETT effect vary between males and females. An equal dosage interval in males and females may not be adequate. ETT efficacy in females may be too limited to offset the risk posed by the QTc prolongation.

2) As compared to other populations, a steeper ranolazine plasma concentration to QTc relationship was found to be notable in patients with liver impairment. What is the basis for assuming that the risk in patients with mild and moderate hepatic impairment is significantly different?

3) Ranolazine is a racemic drug. The similarity of the efficacy and safety of the individual enantiomers would justify the development of such a racemic drug. A difference in pharmacological activity and/or toxicity between the enantiomers results in patients receiving ineffective or toxic drug molecules when a racemic drug is administered. Adequate demonstration of similar efficacy and safety of the individual enantiomers was not provided for ranolazine.

Pharmacology/Toxicology issues

1) The mechanism of action is incompletely described. Data were provided suggesting an effect on cardiac energy metabolism. There is no information as to how other possible mechanisms of action were excluded.

2) The pharmacologic and toxicologic effects of the enantiomers are incompletely described. Data from receptor binding studies and from one single-dose study were presented for the enantiomers. There is no other systematic toxicological characterization

3) Several studies present evidence that the parent drug and several of its major metabolites interact with a variety of cardiac ion channels. The data presented are insufficient to make any conclusions about safety. While it was stated that ECG data were generated for the cardiovascular safety study and several of the general toxicology studies, no ECG data were presented in the submission. Sections of reports entitled "ECG Results" contained only individual animal heart rate information. Other studies are lacking in positive controls, either historic or concurrent, to allow for interpretation. Comparator compounds are also absent. The available data package makes it difficult to form a complete picture of the drug.

4) The major metabolites are incompletely described. There are no receptor binding data apparent and no pharmacological/toxicological characterization other than a few cardiac ion channel studies. Given the proposed maximum recommended doses, the major metabolites could be produced in significant amounts.

5) In the data as presented, ranolazine caused developmental delays including a dose-dependent embryotoxicity in two species, evidence of teratogenicity in two species, and evidence of fertility effects in both sexes. Problems in the studies include:

   - high doses causing excessive toxicity,
   - a lack of histologic data,
   - a lack of sperm assessment parameters,
   - a lack of any pharmacokinetic parameters for pregnant animals or distribution studies to determine partitioning into the placenta, fetus or lacteal secretions.

   One of the developmental studies presented no data for the parameters typically measured. Evidence of reproductive toxicity was also found in the general toxicology studies, despite inconsistent and incomplete pathology reporting.

6) The non-clinical reports overall present inconsistent and incomplete reporting that make evaluation difficult. It further hampers the evaluation that positive controls and comparator compounds are frequently lacking.

Statistical Issues

1) In parallel group pivotal Study CVT 3033, Siberian Site # 710 seems to be an outlier with highly statistically significant treatment effects at trough ($p<0.001$ for Ran 750 mg and $p<0.003$ for Ran 1000 mg). The study is not robust, because after exclusion of Site #710, the treatment effects at trough are small (<18 sec) and no longer significant ($P\geq 0.12$).

2) In pivotal crossover Study CVT 3031, the following critical problems were found:

   - the effect in the first period of ranolazine relative to placebo, if any, was very small and there was no clear dose response.
   - in the second and later periods, there was a large increase in exercise time in favor of ranolazine.
   - the study design did not include washout periods between the treatment periods and there were no baseline measurements for each treatment period.
   - there was insufficient power for testing the possible presence of treatment-by-period interaction and/or differential carry-over effect.

   Arguably, the crossover analysis pooling all periods as performed in the sponsor's primary analysis, tends to bias in favor of ranolazine. Additionally, the study design does not allow determination of whether the significant treatment effects in the sponsor's ANOVA are truly direct drug effects or whether they are influenced by the treatment-by-period interaction or carry-over. The presence of carry-over may suggest that ranolazine has some treatment effect, but this study does not establish whether this effect is statistically significant or not.

Hence, the results of the crossover analysis are very difficult to interpret. Because of the treatment-by-period interaction and possible presence of carry-over, unbiased estimates of treatment effects can be obtained only from the first period data. However, the first period data, at best, show a very small treatment effect that was not statistically significant.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that the reviewers have identified. In conformance with the Prescription Drug User Fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Meg Pease-Fye, Regulatory Health Project Manager, at (301) 594-5312.

Sincerely,

{See appended electronic signature page}

Zelda McDonald
Chief, Project Management Staff
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Zelda McDonald
7/17/03 11:43:52 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

March 24, 2003

NDA 21-526

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

Dear Ms. Karp:

Please refer to your new drug application number 21-526.

The Division of Cardio-Renal Drug Products at the FDA is conducting a meta-analysis to compare the risks for discontinuation for patients receiving either placebo or active treatment as part of placebo-controlled trials of anti-anginal drugs (Cardiovascular Risk In Placebo-Controlled Angina Trials or CRIPCAT). An analysis of this kind was performed previously by the Division using data available from the anti-anginal trials conducted through 1991[1]. Since that time there have been a number of additional trials submitted to the Division for drugs developed to treat angina, and we are interested in repeating the analysis using the larger database. We have tentatively identified 34 NDAs of potential interest, containing around 22,000 enrolled patients, around 5 times as many patients as were available for the earlier analysis. We propose to examine the case report forms for each of the identified dropouts from the trials in these NDAs to ascertain the cause(s) of their discontinuation. Following this, we will unblind each patient to treatment (*i.e.*, placebo or active therapy) and compare the risk of serious adverse events in the treatment and placebo groups. Such an analysis will provide important information regarding the continued use of placebo-controlled trials in the development of anti-anginal medications. Please be assured that no results for any individual drugs will be released as a part of the CRIPCAT project. We would appreciate your cooperation in this undertaking, which can be documented by sending a letter to the Division stating that you will do the following:

a) Give us permission incorporate your data into our database.
b) Assist us to the best of your ability in supplying missing case report forms.

[1] JAMA 265: 1550-1554, 1991

c) Assist us to the best of your ability in supplying treatment codes for the discontinued patients (to be requested after our review of the case report forms).

Thank you for your cooperation.

Sincerely yours,

Douglas Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig.
HFD-110
HFD-110/ADeFelice
sb/6/1/99

INFORMATION REQUEST

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/s/

Doug Throckmorton
3/25/03 08:00:38 AM

8/11/03

To

Carol Karp
Vice President, Regulatory Affairs
CV Therapeutics
3172 Porter Drive
Palo Alto, CA 94304

Re: Telecon on August 7th for Ranexa (ranolazine) 375 and 500 mg extended release tablets.

Dear Ms. Karp:

During the telecon on August 7th 2003, the sponsor requested a copy of the results obtained from the concentration-QTc prolongation analysis. The following is the summary of the results obtained by the FDA reviewer.

Please let us know if you have any further queries.

Sincerely

Venkatesh Atul Bhattaram, Ph.D

Joga Gobburu, Ph.D

Ranolazine Concentation-Delta QTc Relationship in Normal and Hepatically Impaired Subjects.

Methodology:

The data from study CVT 3018 was appended to database (all_qtc_sub2) used by sponsor for QTc analysis.

A two-stage (1) Estimation of Correction factor followed by (2) Estimation of Concentration-QTc prolongation relation was used for describing the ΔQTc (Change in QTc from baseline) and ranolazine concentration relationship.

(1) Estimation of Correction Factor: The QT data from drug free phase (run-in, placebo) were analyzed using the following relationship:

$$QT_{ij} = \alpha_i * RR_{ij}^{\beta i}$$

Where QT_{ij} is the jth QT interval of the ith patient, similarly α_i is the corrected QT and RR is the RR interval and βi is the exponent coefficient of the ith patient.

(2) Estimation of Concentration-QTc relationship: The individual specific β-values derived from Stage-I were merged using SAS into the full database (run-in, placebo, treatment).

Covariate Analysis:

The significance of hepatic impairment was evaluated on the slope of concentration-QTc relationship using the model shown below:

$$\text{Slope (SLP)} = SLP_{normal} + SLP_{mild} + SLP_{moderate}$$

Statistical significance was defined as a change in objective function of atleast 20 points for 1 additional parameter when using the First-Order (FO) estimation procedure in NONMEM.

Results:

The model without threshold concentrations was found to describe the data satisfactorily. The final parameter estimates are shown in Table 1.

Table 1. Summary of Covariate Analyis of Hepatic Status

Model	Slope (msec/ 1 µg/mL)	OBJ	Δ OBJ
Base (No Covariates)		107605.25	
SLP~HEPATIC			
Normal	2.56	107579.56	-25.69
Mild	6.62		
Moderate	7.42		
SLP~HEPATIC			
Normal	2.56	107579.75	-25.50
Mild + Moderate	7.10		

Appears This Way
On Original

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/s/

Jogarao Gobburu
8/11/03 09:05:14 AM
General Correspondence

Atul Bhattaram
8/8/03 03:58:17 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-526

Trade Name: Ranexa
Generic Name: ranolazine
Strengths: 375 mg and 500 mg Tablets

Applicant: CV Therapeutics

Date of Application: December 27, 2002
Date of Receipt: December 30, 2002
Date of Filing Meeting: February 25, 2003
Filing Date: February 28, 2003
User Fee Goal Date: October 30, 2003

Indication(s) requested: Ranexa is indicated for the treatment of chronic angina in patients with severe coronary artery disease, and should be reserved for use in patients in whom other anti-anginals are inadequate or not tolerated

Type of Application: Original (b)(1) NDA ___X___ Original (b)(2) NDA _____
(b)(1) Supplement _____ (b)(2) Supplement _____

Therapeutic Classification: Standard
Resubmission after a withdrawal or refuse to file No
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) N/A

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

Form 3397 (User Fee Cover Sheet) submitted: **YES**
User Fee ID # **N/A**
Clinical data? YES ___X___ NO, Referenced to NDA # _____

Does another drug have orphan drug exclusivity for the same indication? **NO**

Is the application affected by the Application Integrity Policy (AIP)? **NO**

- Does the submission contain an accurate comprehensive index? **YES**
- Was form 356h included with an authorized signature? **YES**
- Submission complete as required under 21 CFR 314.50? **YES**
- If an electronic NDA, does it follow the Guidance? **N/A**
- Patent information included with authorized signature? **YES**
- Exclusivity requested? **NO**
- Correctly worded Debarment Certification included with authorized signature? **YES**

- Financial Disclosure information included with authorized signature? **YES**

- Field Copy Certification (that it is a true copy of the CMC technical section)? **YES**

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? **YES**
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

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

- End-of-Phase 2 Meeting(s)? Date(s) December 12, 1997
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) October 10, 2002
  If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? **YES**

- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support?
  YES

- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support?
  N/A

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? **NO**
  If no, did applicant submit a complete environmental assessment? **YES**
  If EA submitted, consulted to Nancy Sager (HFD-357)? **YES**

- Establishment Evaluation Request (EER) submitted to DMPQ? **YES**

- If parenteral product, consulted to Microbiology Team (HFD-805)? **N/A**

ATTACHMENT
MEMO OF FILING MEETING

DATE: February 25, 2003

BACKGROUND:
Ranexa is indicated for the treatment of chronic angina in patients with severe coronary artery disease, and should be reserved for use in patients in whom other anti-anginals are inadequate or not tolerated

ATTENDEES:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D.	Deputy Director, Division of Cardio-Renal Drug Products
Shari Targum, M.D.	Reviewer, Medical Officer
Maryann Gordon, M.D.	Reviewer, Medical Officer
Albert DeFelice, Ph.D.	Team Leader, Pharmacology
Elizabeth Hausner, D.V.M.	Reviewer, Pharmacology
Hsien-Ming Hung, Ph.D.	Team Leader, Statistics
Valeria Freidlin, Ph.D.	Reviewer, Statistics
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry
Nallaperum Chidamabaram, Ph.D.	Reviewer, Chemistry
Mehul Desai, M.D.	Reviewer, Medical Officer
Salma Lemtouni, M.D.	Reviewer, Medical Officer
Peter Hinderling, M.D.	Reviewer, Clinical Pharmacology and Biopharmocology
Bach Nhi Nguyen, Pharm.D.	Reviewer, Clinical Pharmacology and Biopharmacology
Robert Shibuya, Ph.D.	Pharmacologist, Division of Scientific Investigations
Martin Yau, Ph.D.	Pharmacologist, Division of Scientific Investigations
Tamal Chakraborti, Ph.D.	Pharmacologist, Division of Scientific Investigations
Edward Fromm	Regulatory Health Project Manager
Zelda McDonald	Chief, Project Management Staff
Meg Pease-Fye	Regulatory Health Project Manager

ASSIGNED REVIEWERS:

Discipline	**Reviewer**	**Completion Date**
Medical (efficacy):	Shari Targum	Mid August, 2003
Medical (safety):	Maryann Gordon	Mid August, 2003
Statistical:	Valeria Freidlin	September 1, 2003
Pharmacology:	Elizabeth Hausner	September 1, 2003
Statistical Pharmacology:	N/A	
Chemist:	Nallaperum Chidamabaram	September 1, 2003
Environmental Assessment (if needed):	Nallaperum Chidamabaram	September 1, 2003
Biopharmaceutical:	Peter Hinderling	September 1, 2003
Microbiology, sterility:	N/A	
Microbiology, clinical (for antimicrobial products only):	N/A	
DSI:	To be determined	
Regulatory Project Manager:	Meg Pease-Fye	
Other Consults:	To be determined	

Per reviewers, are all parts in English or English translation? **YES**

Applicant: CV Therapeutics

Subject: NDA 21-526
Ranexa (ranolazine) Tablets, 375 mg and 500 mg

The meeting opened with Dr. Throckmorton recommending that careful review of the proposed labeling is the best way to identify any deficiencies of the submission. Reviewers need to determine what data the Sponsor has for any given part of the label and communicate early with the Sponsor. Reviewers are urged not to wait until last minute to find sections to support label deficiencies.

The proposed indication is for chronic angina in severe coronary artery disease. This drug is known to prolong QT and there are pre-clinical signals of pro-arrhythmic potential. The resistant therapy claim is the approach to approval for use as a second line drug.

The goal date is October 30, 2003 and will be an Office sign off. It is too early to determine if this will go to Advisory Committee although it is a candidate. The reviews need to be done 6 weeks before, taking us to mid September, unless it goes to the Advisory Committee in September and then the reviews will need to be done by mid August.

Disciplines
Chemistry: There are six sites and one has been inspected, so only five sites are still needed for inspection. One possible deficiency is that the Sponsor has asked for [ ] expiration but has only sent stability data to support [ ] expiration date.

PharmTox: Carcinogenicity studies have been done. One major issue is that the fertility/development study was unacceptable for a number of reasons. The study showed a 30% decrease in male fertility, based only on dosing and mating, a very unusual finding for even a known reproductive toxicant. Also, the teratogenicity studies indicate that the high doses were too high resulting in maternal mortality. Thus there were insufficient numbers of subjects to evaluate. Reproductive and developmental effects are uncharacterized with the available data. Clinical signs were consistent across species and one possible explanation of the signs is through opioid receptor binding. There may be a dependence potential to be considered. The drug has been shown to bind *in vitro* to numerous receptors, with sometimes variable and conflicting results. We need a detailed characterization of opioid receptor binding. Also, for the proposed mechanism of action, we need a detailed explanation from the Sponsor as to how they eliminated all the possible mechanisms and combinations of mechanism to focus on the proposed labeling version. The Sponsor also needs to identify for the reviewers the studies critical to their assertion about the pre-clinical electrophysiology.

Biopharmocology: the assay validation reports of 6 studies are not available. Also, not all reports on the cross validation of the different assay methods appear to be available. Tablet dissolution methodologies are not described with individual reports; only a summary was provided. The summary contains mean data, but not individual data. The dissolution data are pivotal because the Sponsor requests a Biowaiver for the lower 375mg strength tablet. An inspection of the study site that performs the bioequivalence study comparing the service and commercial forms of the higher strength 500mg tablet and of the laboratory measuring the plasma ranolazine concentrations of the study was recommended.

There seems to be no description about how the changes in the QT interval determined in the different studies. The Sponsor provided no justification for using the racemic drug instead of a single enantiomer (eutomer versus distomer).

A possible activity of the metabolites in humans cannot be excluded, even though in pre-clinical models the activity of the metabolites was clearly smaller than that of the parent compound. In the animal studies, C_{max} is

seen from 0.5 – 1 hour but clinical signs may be seen for several hours, suggesting a precursor product relationship or saturation of clearance. This analysis is complicated, in that the drug is a racemate and no information on the relevant activities (*e.g.*, effect on QT) was submitted.

Medical: There were controlled and uncontrolled clinical trials. Many of the uncontrolled trials had protocols; one was missing and Sponsor is sending a copy of it.

Proposed labeling:
In vitro, this drug is an inhibitor of enoyl hydratase, has alpha adrenergic agonist activity, and calcium channel inhibiting properties as well as interacting with other receptors and possibly other enzymes.

- Pharmacokinetics: Dose and concentration dependent QTc prolongations were observed. The analysis by the Sponsor indicated that the increase in QTc was about 2msec/1000ng/mL with no dependency on gender in the population investigated. Patients with moderate liver impairment (Child-Pugh Grade B) showed an increase of 15msec/1000ng/ml. Exposure to the parent drug in the patients with moderate liver impairment was not significantly greater than that in other subpopulations with normal hepatic function. These subpopulations did not show the excessive prolongations of the QTc interval. Thus, it is possible that the larger increase in the QTc interval observed in the hepatic patients is caused by a metabolite that is generated in larger amounts in moderate liver impairment than in subjects with normal hepatic function. In the labeling proposed by the Sponsor, administration of ranolazine is contraindicated in patients with moderate liver impairment. *In vitro* and *in vivo* studies indicate that the drug is a substrate of CYP3A4 and 2D6, and an inhibitor of CYP3A4 and P-Glycoprotein (Pgp). These properties explain why ranolazine's pharmacokinetics (PK) are sensitive to co-administered CYP3A4-and 2 D6 inhibitors and why the PK of other 3A4-and Pgp-substrates are susceptible to co-administered ranolazine.

- There were notched T-waves although there was no indication of how this was assessed. We would also want to know how they characterize the morphologic changes.

- Clinical studies: Primary endpoints were stress tests and other endpoints tied to angina. The label states that the drug works in patients who can not take other anti-anginals, and the indication is for those in whom anti-anginals are inadequate or not well tolerated. In terms of reactive airway disease, numbers in this subgroup are small relative to the exposed population and therefore might not be supportive of the labeling data.

CLINICAL	FILE __X__	REFUSE TO FILE _____	
• Clinical site inspection needed:		To be determined	
• Advisory Committee Meeting needed?		YES, date if known _____	NO
CLINICAL MICROBIOLOGY	FILE _____	REFUSE TO FILE _____	**N/A**
STATISTICS	FILE __X__	REFUSE TO FILE _____	
BIOPHARMACEUTICS	FILE __X__	REFUSE TO FILE _____	
• Biopharm. inspection needed:		**YES**	

PHARMACOLOGY FILE __X__ REFUSE TO FILE ____

- GLP inspection needed: **NO**

CHEMISTRY FILE __X__ REFUSE TO FILE ____

- Establishment(s) ready for inspection? **YES**
- Microbiology **N/A**

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

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

_____ No filing issues have been identified.

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

REVIEW ISSUES IDENTIFIED:

- [redacted] expiry vs. [redacted] stability data submitted
- Inadequate reprotox studies
- Inadequate opioid receptor binding characterization
- QT effect not fully characterized
- Racemate parent compounds/active metabolites
- Difference in effect of QT in hepatic impairment

_____
Regulatory Project Manager, HFD-110

C:\Data\Wpfiles\FilingSummary2.doc
LRipper/1-13-03

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/s/

Doug Throckmorton
3/6/03 01:54:28 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Michael Koren, M.D.
Jacksonville Center for Clinical Research
4085 University Boulevard South, Suite 1
Jacksonville, Florida 32216

AUG 11 2003

Dear Dr. Koren:

Between June 6 and 13, 2003, Ms. Barbara Carmichael, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations:

Protocol 3031 entitled: "A Double-Blind, Placebo-Controlled, 4-Period Cross-Over, Multiple-Dose Study of Ranolazine SR as Monotherapy for Chronic Stable Angina Pectoris at Doses of 500 mg bid, 1000 mg bid, and 1500 mg bid;" and

Protocol 3033 entitled: "A Double-Blind, Randomized, Stratified, Placebo-Controlled, Parallel Study of Ranolazine SR at Doses of 750 mg Twice a Day and 1000 mg Twice a Day in Combination with Other Anti-Anginal Medications in Patients with Chronic Stable Angina Pectoris" of the investigational drug ranolazine SR, performed for CV Therapeutics.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Carmichael presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

You did not adhere to the approved protocol (21 CFR 312.60) in that subject 7309 used omeprazole while on protocol 3033. Omeprazole was prohibited by the protocol because of its ability to inhibit cytochrome P450 3A4.

Please make appropriate corrections in your procedures to assure that the finding noted above is not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Carmichael during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Joseph P. Salewski
Acting Director
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3000720100
Field Classification: VAI
Headquarters Classification:
_____1)NAI
__X__2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
__X_failure to adhere to protocol (05)
Deficiency Codes: **5**

cc:
HFA-224
HFD-110 Doc.Rm. NDA# 21-526
HFD-110 Review Div.Dir. Throckmorton
HFD-110 MO Targum
HFD-110 PM Pease-Fye
HFD-47c/r/s/ GCP File # 9305
HFD-47 Shibuya
HFR-SE250 DIB Gallant
HFR-SE250 Bimo Monitor Torres
HFR-SE250 Field Investigator Carmichael
GCF-1 Seth Ray

r/d: (RS/7/25/03)
reviewed:JPS:8/1/03
f/t:ml:8/4/03
o:**\RS\NDA 21-526\Koren.doc**

Reviewer Note to Rev. Div. M.O.

- For protocol 3031, this site enrolled 6 subjects and completed 5. For protocol 3033, this site enrolled and completed 6 subjects.
- All subjects consented to the trial.
- Records from two subjects from each protocol were inspected in detail.
- One minor protocol deviation was documented.
- Data appear acceptable.

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/s/

Joseph Salewski
8/19/03 08:50:29 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL - 3 2003

Peter Hanley, M.D.
Medical Group of Fort Wayne
7836 W. Jefferson Avenue
Fort Wayne, Indiana 46802

Dear Dr. Hanley:

On May 27, 2003, Mr. William Brubaker, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations (protocols #CVT 3031 and 3033 entitled: "A Double-Blind, Placebo-Controlled, 4-Period Cross-Over, Multiple-Dose Study of Ranolazine SR as Monotherapy for Chronic Stable Angina Pectoris at Doses of 500 mg bid, 1000 mg bid and 1500 mg bid") of the investigational drug Ranexa (ranolazine), performed for CV Therapeutics. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Brubaker during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me, by letter at the address given below.

Sincerely,

Joseph P. Salewski

Joseph P. Salewski
Acting Director
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI:3004013415
Field Classification: NAI
Headquarters Classification:
__x__1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-110 Doc.Rm. NDA#21526
HFD-110 Review Div.Dir.
HFD-110 MO (Targum)
HFD-110 PM (Peasefye)
HFD-47c/r/s/ GCP File #10920
HFD-47 Shibuya
HFD-47 Storms
HFR-CE750 DIB (Dempster)
HFR-CE750 Bimo Monitor (Bellamy)
HFR-CE7550 Field Investigator (Brubaker)
GCF-1 Seth Ray

r/d:KMS:6.27/03
reviewed:AEH:6/30/03
f/t: sg: 7/30/03; ML: 7/1/03
o:**KMS\hanleyltr**

Reviewer Note to Rev. Div. M.O.

- This site enrolled 11 subjects in CVT3031 and 6 subjects in CVT3033.
- All subjects met inclusion criteria.
- All ECG were verified with the ECG Core Laboratory report.
- All subjects received informed consent.
- Data from this site may be used in support of the pending NDA application.

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/s/

Joseph Salewski
7/11/03 08:25:47 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 43,735

8/31/01

CV Therapeutics, Inc.
Attention: Ms. Allene M. Dodge
3172 Porter Drive
Palo Alto, CA 94304

Dear Ms. Dodge:

Reference is made to your correspondence dated August 10, 2001, requesting a waiver for pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver is justified for Ranolazine Sustained Release (SR) Tablets for chronic angina pectoris for all pediatric age groups covered by the Pediatric Rule.

Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Raymond Lipicky
8/31/01 12:27:17 PM

✓ Transcript and Quick minutes

____ Sponsor's Briefing Material

____ FDA'S Briefing Material

393 PAGES REMOVED. SEE THE ADVISORY COMMITTEE MEETING INFORMATION LOCATED ON THE FDA WEBSITE BELOW:

http://www.fda.gov/ohrms/dockets/ac/