

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-359

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**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

NAME OF APPLICANT / NDA HOLDER
Cellegy Pharmaceuticals, 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)
Cellegesic

ACTIVE INGREDIENT(S)
Nitroglycerin

STRENGTH(S)
0.4% ointment

DOSAGE FORM
Ointment

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
5,504,117

b. Issue Date of Patent
4/2/1996

c. Expiration Date of Patent
5/27/2014

d. Name of Patent Owner
Cellegy Pharmaceuticals, Inc.

Address (of Patent Owner)
349 Oyster Point Boulevard, Suite 200

City/State
South San Francisco, CA

ZIP Code
94080

FAX Number (if available)
650-616-2222

Telephone Number
650-616-2200

E-Mail Address (if available)
webmaster@cellegy.com

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.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

N/A

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

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 attached pages for additional 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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.	

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
	5/27/04

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 K. Michael Forrest Cellegy Pharmaceuticals, Inc.	
Address 349 Oyster Point Boulevard, Suite 200	City/State South San Francisco, CA
ZIP Code 94080	Telephone Number 650-616-2200
FAX Number (if available) 650-616-2222	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.

3. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

3. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

3. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

3. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

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**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

NAME OF APPLICANT / NDA HOLDER
Cellegy Pharmaceuticals, 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)
Cellegesic

ACTIVE INGREDIENT(S)
Nitroglycerin

STRENGTH(S)
0.4% ointment

DOSAGE FORM
Ointment

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.

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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
5,693,676

b. Issue Date of Patent
12/2/1997

c. Expiration Date of Patent
5/27/2014

d. Name of Patent Owner
Cellegy Pharmaceuticals, Inc.

Address (of Patent Owner)
349 Oyster Point Boulevard, Suite 200

City/State
South San Francisco, CA

ZIP Code
94080

FAX Number (if available)
650-616-2222

Telephone Number
650-616-2200

E-Mail Address (if available)
webmaster@cellegy.com

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.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

N/A

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

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 attached pages for additional 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.)
 Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

5. No Relevant Patents

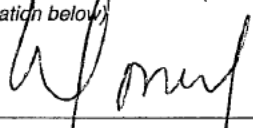
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably 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.*

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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

 5/27/04

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
K. Michael Forrest
Cellegy Pharmaceuticals, Inc.

Address
349 Oyster Point Boulevard, Suite 200

City/State
South San Francisco, CA

ZIP Code
94080

Telephone Number
650-616-2200

FAX Number (if available)
650-616-2222

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.

3. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

3. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

.. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

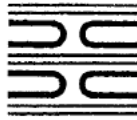
4. Method of Use	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one 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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

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DUPLICATE



CELLEGY
PHARMACEUTICALS INC

RECEIVED
OCT 20 2004
CDR / CDER

RECEIVED

October 1, 2004

OCT 21 2004

DDR-110 / CDER

NEW CORRESP

N 000 (C)

Norman Stockbridge, M.D.
Director, CardioRenal Drug Products Division
FDA
WOC2, RM5033
Mail Stop: HFD-110
Rockville, MD 20852

Re: NDA 21-359 21 C.F.R. 314.52 Notice of certification of invalidity or noninfringement of a patent

Dr. Stockbridge,

I certify that a notice under 21 C.F.R 314.52 has been provided to each owner of patent US 5, 186,938 and the holder of the approved application for the drug product which is claimed by the patent. Key Pharmaceuticals is the owner of the patent and, according to the Orange Book, the holder of the application. Documentation of receipt of the notice by Key Pharmaceuticals is attached herewith in the form of the Receipt for Registered Mail and the Domestic Return Receipt provided by the US Postal Service. I believe Cellegy is now in full compliance with the provisions of 21 C.F.R 314.52.

Sincerely,

K. Michael Forrest

Registered No. **FB34618438845** Date Stamp **SEP 16 2004**

To Be Completed By Post Office	Reg. Fee \$ 7.50	
	Handling Charge \$ 0.23	Return Receipt \$ 1.75
	Postage \$ 0.23	Restricted Delivery
	Received by <i>[Signature]</i>	

Customer Must Declare Full Value \$ **0**

With Postal Insurance
 Without Postal Insurance

Domestic Insurance up to \$25,000 included in the fee. International indemnity is limited. (See Reverse).

San Francisco Postal Retail Store

To Be Completed By Customer (Please Print) All Entries Must Be in Ballpoint or Typed	FROM	K. Michael Forrest
		Cellagy Pharmaceuticals Inc.
		349 Oyster Point Blvd Suite 200
		South San Francisco, CA 94080
	TO	Thomas Sabatino, Jr. Esq.
		Key Pharmaceuticals
		2000 Galloping Hill Rd.
		Kenilworth, NJ 07033-0530

PS Form 3806, Receipt for Registered Mail Copy 1 - Customer
 June 2002 (See Information on Reverse)

For delivery information, visit our website at www.usps.com®

Is your RETURN ADDRESS completed on the reverse side?

SENDER:

- Complete items 1 and/or 2 for additional services.
- Complete items 3, 4a & b.
- Print your name and address on the reverse of this form so that we can return this card to you.
- Attach this form to the front of the mailpiece, or on the back if space does not permit.
- Write "Return Receipt Requested" on the mailpiece below the article number.
- The Return Receipt will show to whom the article was delivered and the date delivered.

I also wish to receive the following services (for an extra fee):

- Addressee's Address
- Restricted Delivery

Consult postmaster for fee.

3. Article Addressed to: Thomas Sabatino, Jr. Esq. ERP & General Counsel Key Pharmaceuticals 2000 Galloping Hill Road Kenilworth, NJ 07033-0530	4a. Article Number FB34618438845
5. Signature (Addressee)	4b. Service Type ☒ Registered ☐ Insured ☐ Certified ☐ COD ☐ Express Mail ☐ Return Receipt for Merchandise
6. Signature (Agent) <i>[Signature]</i>	7. Date of Delivery 9/20/04
PS Form 3821, December 1991 *U.S. GPO: 1993-352-714	8. Addressee's Address (Only if requested and fee is paid)

DOMESTIC RETURN RECEIPT

Thank you for using Return Receipt Service.



Fax Transmittal Sheet

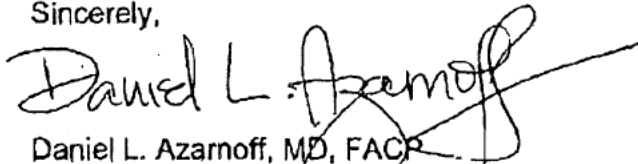
DATE:	8/30/04	TOTAL PAGES:	2
		(INCL. COVER SHEET)	
TO:	<i>Darryl Allis,</i> <i>Project Manager</i>	FAX NO.:	301.594.5494
COMPANY:	FDA		
FROM:	Daniel L. Azarnoff, MD, FACP Clinical/Regulatory Affairs, Consultant	DIRECT PHONE NO:	650.616.2200
		DIRECT FAX NO:	650.616.2222

To Mr. Allis,

The attached letter from K. Michael Forrest, CEO provides Cellegy's commitment to submit an answer to your request regarding our patent certification.

We have requested the validation of the nitroglycerin assay used for the bioavailability study from the laboratory that performed it, and will provide it when we receive it.

Sincerely,



Daniel L. Azarnoff, MD, FACP
Clinical/Regulatory Affairs-Consultant

Important Confidentiality Notice

The information accompanying this facsimile transmission is intended only for the use of the individual or entity to which it is addressed. The information may be legally privileged, confidential and exempt from disclosure under applicable law. If the reader of this message is not the intended recipient, or the employee or agent responsible for delivering the message to the intended recipient, you are hereby notified that any dissemination, distribution or copying of the communication is strictly prohibited.

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If all pages are NOT received please call the above telephone number for assistance. Thank you.

PLEASE DELIVER AS SOON AS POSSIBLE



K. Michael Forrest
President and Chief Executive Officer

August 30, 2004

Norman Stockbridge, M.D.
Director, CardioRenal Drug Products Division
FDA
WOC2, RM5033
Mail Stop: HFD-110
Rockville, MD 20852

Re: NDA 21-359 §314.50 Paragraph IV Certification

Dr. Stockbridge,

You have brought to our attention FDA Application No. 020145 for the "NITRO DUR" product. The electronic orange book indicates the "NITRO DUR" product is covered by U.S. Patent Number 5,186,938.

I, K. Michael Forrest, certify that U.S. Patent Number 5,186,938 will not be infringed by the manufacture, use, or sale of Cellegesic™ nitroglycerin ointment for which this application is submitted. We intend to comply with the requirements under §314.52(a) with respect to providing notice to each owner of the 5,186,938 patent or their representatives and to the holder of the approved application for the drug product which is claimed by the patent and with the requirements under §314.52(c) with respect to the content of the notice.

Sincerely,

A handwritten signature in black ink, appearing to read 'K. Michael Forrest'.

K. Michael Forrest

**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

NAME OF APPLICANT / NDA HOLDER
Cellegy Pharmaceuticals, 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)
Cellegesic

ACTIVE INGREDIENT(S)
Nitroglycerin

STRENGTH(S)
0.4% ointment

DOSAGE FORM
Ointment

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 5,504,117	b. Issue Date of Patent 4/2/1996	c. Expiration Date of Patent 5/27/2014

d. Name of Patent Owner Cellegy Pharmaceuticals, Inc.	Address (of Patent Owner) 349 Oyster Point Boulevard, Suite 200	
	City/State South San Francisco, CA	
	ZIP Code 94080	FAX Number (if available) 650-616-2222
	Telephone Number 650-616-2200	E-Mail Address (if available) webmaster@cellegy.com

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) N/A	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

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

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)

- 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 attached pages for additional 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.)
 Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

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

5/27/04

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

K. Michael Forrest
Cellegy Pharmaceuticals, Inc.

Address

349 Oyster Point Boulevard, Suite 200

City/State

South San Francisco, CA

ZIP Code

94080

Telephone Number

650-616-2200

FAX Number (if available)

650-616-2222

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.

3. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

3. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

3. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

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<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

60212220 v1

Patent and Exclusivity Search Results from query on Appl No 020145 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020145	001	5186938	FEB			

Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(c)(3)(5).
 2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
 3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
 4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.
-

[View a list of all patent use codes](#)

[View a list of all exclusivity codes](#)

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FDA/Center for Drug Evaluation and Research
 Office of Generic Drugs
 Division of Labeling and Program Support
 Update Frequency:

- Orange Book Data - **Monthly**
- Orange Book Data Updated Through September,
- Orange Book Patent Data Only - **Daily**
- Patent Data Last Updated: October 28, 2004

**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

NAME OF APPLICANT / NDA HOLDER
Cellegy Pharmaceuticals, 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)
Cellegesic

ACTIVE INGREDIENT(S)
Nitroglycerin

STRENGTH(S)
0.4% ointment

DOSAGE FORM
Ointment

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 5,693,676	b. Issue Date of Patent 12/2/1997	c. Expiration Date of Patent 5/27/2014
d. Name of Patent Owner Cellegy Pharmaceuticals, Inc.	Address (of Patent Owner) 349 Oyster Point Boulevard, Suite 200	
	City/State South San Francisco, CA	
	ZIP Code 94080	FAX Number (if available) 650-616-2222
	Telephone Number 650-616-2200	E-Mail Address (if available) webmaster@cellegy.com
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) N/A	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	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

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?	
1	(see attached pages for additional claims)	☒ 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.) Cellestic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.	

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

5/27/04

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

K. Michael Forrest
Cellegy Pharmaceuticals, Inc.

Address

349 Oyster Point Boulevard, Suite 200

City/State

South San Francisco, CA

ZIP Code

94080

Telephone Number

650-616-2200

FAX Number (if available)

650-616-2222

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.

Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

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<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

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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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

4. Method of Use	
<i>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:</i>	
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.) Cellegesic nitroglycerin ointment is indicated for relief of pain associated with anal fissure.

60212611 v1

TOWNSEND
and
TOWNSEND
and
CREW
LLP

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June 1, 2001

ATTORNEY CLIENT PRIVILEGED

VIA FACSIMILE 650-616-2222

Daniel L. Azarnoff
Senior Vice President of
Clinical & Regulatory Affairs
Cellegy Pharmaceuticals, Inc.
349 Oyster Point Boulevard, Suite 200
South San Francisco, CA 94080

Re: Expiration dates of the Gorfine Patents, U.S. Patent Nos. 5,504,117
and 5,693,676

Dear Dan:

U.S. Patent No. 5,504,117, ("the '117 patent") was filed on May 27, 1994, and issued April 2, 1996. Under 35 U.S.C. 154(c)(1):

[t]he term of a patent that is in force on
or that results from an application filed before the date that is
6 months after the date of the enactment of the Uruguay Round
Agreements Act shall be the greater of the 20-year term as
provided in subsection (a), or 17 years from grant, subject to
any terminal disclaimers.

Thus, under the 35 U.S.C. § 154, the '117 patent will expire the longer of, 20 years from filing
the application or 17 years from grant. Therefore, the '117 will expire on May 27, 2014.

With regard to U.S. Patent No. 5,693,676, ("the 676 patent"), which was filed on June 20, 1996,
and which issued on December 2, 1997, 35 U.S.C 154(a)(2) applies and states:

[s]ubject to the payment of fees under this title,
such grant shall be for a term beginning on the date on which the
patent issues and ending 20 years from the date on which the
application for the patent was filed in the United States or, if
the application contains a specific reference to an earlier filed
application or applications under section 120, 121, or 365(c) of
this title, from the date on which the earliest such application
was filed.

TOWNSEND
and
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and
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LLP

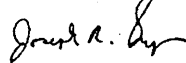
June 1, 2001
Page 2

The '676 patent claims priority to U.S. Application No. 371,088, filed January 10, 1995, and U.S. Application No. 250,555, filed May 27, 1994. The '676 patent claims priority to these previous applications under 35 U.S.C § 120.

Thus, under the 35 U.S.C. § 154, the '676 patent will expire 20 years from its earliest claimed priority. The '676 patent will thus expire on May 27, 2014.

Please be aware that in calculating these expiration dates we have not considered whether the patents are entitled to patent term adjustments or extensions under applicable Federal Law. If you have any questions regarding these expiration dates, please contact me.

Very truly yours,



Joseph R. Snyder

JS/sgk
cc: Christin Piazza
William M. Smith, Esq.
SF 1231146 v1

EXCLUSIVITY SUMMARY

NDA # 021359

SUPPL # 0

HFD # 170

Trade Name RECTIV

Generic Name nitroglycerin ointment 0.4%

Applicant Name Prostrakan

Approval Date, If Known June 21, 2011

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)(2)

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?

3

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# 20145

NITRO-DUR

NDA# 19970

NITROGLYCERIN IN DEXTROSE 5%

NDA# 21135

NITROSTAT (see Orange Book for additional approved nitroglycerin products)

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 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"):

Study REC-C-001,

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 # 45326 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:

Name of person completing form: Christopher Hilfiger
Title: Regulatory Project Manager
Date: June 21, 2011

Name of Office/Division Director signing form: Rigoberto Roca, M.D.
Title: Deputy Division Director

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/

CHRISTOPHER M HILFIGER
06/21/2011

RIGOBERTO A ROCA
06/21/2011

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

DA/BLA#: 21359 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DAARP PDUFA Goal Date: 3/31/10 Stamp Date: 9/30/2010

Proprietary Name: Rectogesic

Established/Generic Name: nitroglycerin 0.4%

Dosage Form: ointment

Applicant/Sponsor: ProStrakan

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

- (1) _____
- (2) _____
- (3) _____
- (4) _____

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

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: relief of pain associated with chronic anal fissures

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

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

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

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

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

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

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

Q3: Does this indication have orphan designation?

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

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

- Yes: (Complete Section A.)
- No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

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

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

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

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

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

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit*	Ineffective or unsafe [†]	Formulation failed ^A	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	0 yr. 0 mo.	0 yr. 0 mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

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

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

- # Not feasible:
 - Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): We are waiving the pediatric study requirement for efficacy in ages 0 to 4 years because necessary studies are impossible or highly impracticable. This is because efficacy assessment is unreliable in that age range

- * Not meaningful therapeutic benefit:
 - Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

Ineffective or unsafe:

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

Δ Formulation failed:

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

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

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

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
☐ Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	
☒ Other	(b) (4) yr. 0 mo.	(b) (4) yr. 0 mo.	☒	☐	☐	☐	
☒ Other	(b) (4) yr. 0 mo.	16 yr. 0 mo.	☒	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	
Date studies are due (mm/dd/yy): 16 months post FDA protocol review							

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

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

* Other Reason: _____

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

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

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

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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

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

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

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

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

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

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

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

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

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

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

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

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

Attachment A

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

Indication #2: _____

Q1: Does this indication have orphan designation?

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

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

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

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

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

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

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

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

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

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

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

Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): _____

Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

Δ Formulation failed:

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

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the eRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmts@fda.hhs.gov) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

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

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
Date studies are due (mm/dd/yy): _____							

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

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

* Other Reason: _____

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

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

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

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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

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

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

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

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

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

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

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

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
☐ Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐ All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

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

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

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

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

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

(Revised: 6/2008)

CELLEGESIC PEDIATRIC PARTIAL WAIVER REQUEST

Product name: CELLEGESIC™ (nitroglycerin) 0.4% Ointment

IND and NDA numbers: IND 45,326 and NDA 21-359

Applicant: ProStrakan, Inc.

Indication(s): Treatment of moderate to severe pain associated with chronic anal fissure.

1. What pediatric age group(s) is included in your waiver request?

Children less than (b) (4) years of age.

2. With regard to each age group for which a waiver is sought, state the reason(s) for waiving pediatric assessment requirements with reference to applicable statutory authority (i.e., one of the options (a) – (d) listed below – choose all that apply):
 - a) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients in that age group, and is not likely to be used in a substantial number of patients in that age group.
 - b) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed.

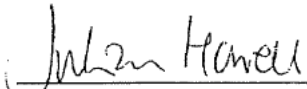
A waiver is requested for this pediatric age group because the pharmacological benefit of nitroglycerin is through pain reduction. In adults this has been measured as daily average pain. ProStrakan does not believe that it is feasible to assess daily average pain from anal fissure and potentially from headache in non-verbalizing children (less than (b) (4) years of age). Although tools exist to measure behavioral response to pain, these have been used to measure pain at a point incidence in time and not as an average.

(b) (4)

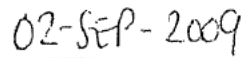
- c) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in that age group.
 - d) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.
3. Provide evidence that the statutory reason(s) for waiver of pediatric studies have been met (not necessary if the 2(a) category is checked).

4. Applicant Certification

The data and information in this pediatric studies deferral request have been reviewed and, to the best of my knowledge, are true and accurate.



Dr. Julian Howell
Head of Clinical Development, Strakan



Date

REFERENCES

von Baeyer, C.L., 2006. Children's self-reports of pain intensity: Scale selection, limitations and interpretation. *Pain Res Manage*, 11(3), pp. 157-162.

CELLEGESIC PEDIATRIC PARTIAL DEFERRAL REQUEST

Product name: CELLEGESIC™ (nitroglycerin) 0.4% Ointment

IND and NDA numbers: IND 45,326 and NDA 21-359

Applicant: ProStrakan Inc

Indication(s): Treatment of moderate to severe pain associated with chronic anal fissure.

1. What pediatric age groups are included in your deferral request?

Children (ages (b) (4) years inclusive)

Adolescents (ages (b) (4) years inclusive)

2. Reason(s) for requesting deferral of pediatric studies in patients (b) (4) years of age inclusive:

a) Adult studies have been completed and are ready for approval.

A confirmatory Phase III clinical trial is provided in this NDA resubmission (APT study, REC-C-001). Data from three further Phase III clinical studies were submitted to the FDA on June 30, 2004 (study reports NTG 98-03-01, NTG 00-03-01 and CP 125 03-03-01).

b) Additional postmarketing safety data needed (describe)

c) Nature and extent of pediatric data needed (explain)

Data from a clinical trial is needed to demonstrate the safety and feasibility of application of CELLEGESIC™ (nitroglycerin) 0.4% Ointment in the pediatric population.

(b) (4)

The Applicant plans to pursue the opportunity to qualify for pediatric exclusivity under section 505A of the Federal Food, Drug, and Cosmetic Act, and will be seeking the Division's advice in this regard.

d) Evidence provided of technological problems with development of a pediatric formulation

e) Difficulty in enrolling pediatric patients (provide documentation)

f) Other (specify)

3. What pediatric age group is not included in your deferral request?

Children less than (b) (4) years of age.

4. Reason for not including the pediatric age group listed in number 3 in the deferral request.

A waiver is requested for this pediatric age group because the pharmacological benefit of nitroglycerin is through pain reduction. In adults this has been measured as daily average pain. ProStrakan does not believe that it is feasible to assess daily average pain from anal fissure and potentially from headache in non-verbalizing children (less than (b) (4) years of age). Although tools exist to measure behavioral response to pain, these have been used to measure pain at a point incidence in time and not as an average. (b) (4)

A waiver for this age group is presented separately.

5. Has a pediatric plan been submitted to the Agency?

A pediatric studies plan is included in Attachment 1.

As noted above, the Applicant plans to pursue the opportunity to qualify for pediatric exclusivity under section 505A of the Federal Food, Drug, and Cosmetic Act with the Division.

6. Suggested deferral date for submission of studies.

The following timelines are proposed (by month end):

Protocol submission:

Study start:

Final report:

(b) (4)

APPLICANT CERTIFICATION

The data and information in this pediatric studies deferral request have been reviewed and, to the best of my knowledge, are true and accurate.

Julian Howell

Dr. Julian Howell
Head of Clinical Development, Strakan

02-SEP-2009

Date

ATTACHMENT 1

Pediatric Studies Plan For CELLEGESIC™ (nitroglycerin) 0.4% Ointment

PEDIATRIC STUDIES PLAN

For

CELLEGESIC™ (nitroglycerin) 0.4% Ointment

Introduction

Anal fissure is a solitary ulcer in the squamous epithelium of the anus. A typical anal fissure is located just distal to the muco-cutaneous junction, usually in the posterior midline. Anal fissure causes intense anal pain, especially upon defecation and for one to two hours afterwards [Nelson 2003, Nelson 2009]. The presence of an anal fissure is associated with an elevated intra-anal pressure caused by hypertonicity of the internal anal sphincter. Increased anal sphincter pressure diminishes blood flow to the anoderm. The pain caused by the fissure is thought to be due to ischemia of the anoderm. Reduction of internal anal sphincter pressure has been associated with relief of pain and healing of the fissure without recurrence [Nelson 2003].

There are no approved drugs available in the United States (US) for the treatment of anal fissure. The surgical procedure, lateral internal sphincterotomy, reduces anal sphincter tone and relieves anal pain, but may lead to impairment of continence in up to 30% of patients [Lund 2006]. 'Pharmacological sphincterotomy', through the application of nitroglycerin (NTG) ointment into the anal canal, however, lowers sphincter pressure without a significant risk of anal incontinence. NTG is converted in tissue to nitric oxide (NO), a second messenger that relaxes smooth muscle of the internal anal sphincter and increases anoderm blood flow [Schouten 1996]. The expression of NO synthase, the enzyme that synthesizes NO *in vivo*, is decreased in the anal sphincter muscle of fissure patients, and this deficiency may be responsible for the increase in anal sphincter tone and a predisposition to fissure relapse. These pharmacodynamic effects form the basis for the use of NTG to treat the pain from a chronic anal fissure.

Pathophysiology and Clinical data in Pediatrics

Anal fissure has been described in children and adolescents with a peak incidence described at 6 to 24 months [Cook 1988]. The symptoms and physical appearance of anal fissure in children is the same as in adults; similarly aetiology in the pediatric population is thought to be the same as in adults. NTG is used in children as a diagnostic and antihypertensive agent, both sublingually and intravenously. The same physiological response to NTG is seen in children as in adults [Oskarsson 2002; Tobias 2002]. Response to topically applied NTG has also been measured and reported [Tander 1999]. In this study 0.2% NTG was applied to 31 patients and maximal anal resting pressure measured; a mean fall in pressure from 27.9 cm H₂O to 12.65 cm H₂O was noted.

There are few studies reporting use of topical NTG in pediatric patients. Simpson et al (2003) investigated the use of 0.1% and 0.05% NTG ointment in the treatment of chronic anal fissures in children in a study involving 15 patients. The median age of the children in this study was 6 years (range 3-13 years) who had a median duration of symptoms of 9 months. Parents were trained to dispense an amount of NTG ointment equivalent to 100 mg and 50 mg of 0.1% and 0.05% NTG respectively, which was applied twice daily for 8 weeks. A further course of treatment was offered to patients who did not respond initially.

At the end of the study, all seven patients in the 0.05% group and 5/8 in the 0.1% group had anal fissures which had healed. One patient in each group experienced an isolated headache in the first few days of treatment, however, this did not affect compliance. No other side effects were reported. Three patients in the 0.1% group received another course of treatment and two of these patients had fissure healing during this second treatment course. There was no evidence of recurrence during the median follow-up period of 4.5 months in the remaining 14 children.

Tander et al (1999) investigated the use of NTG ointment in children with anal fissures in a randomised, double-blind placebo-controlled trial. Patients were allocated to receive 10% lidocaine ointment, 0.2% NTG ointment or placebo for 8 weeks. Thirty-one patients were treated with 0.2% NTG ointment which was applied to the lower anal canal twice daily. Complete healing was observed in 26/31 patients in the NTG group (84%) in contrast to only 7/14 and 6/17 in lidocaine and placebo groups respectively ($P < 0.001$). It was also reported that 94% of patients reported total relief of symptoms in NTG group compared with only 50% and 35% in the lidocaine and placebo groups.

In terms of tolerability, one patient in the NTG group became fecally incontinent, however this resolved spontaneously when the product was discontinued for two weeks. No headaches were reported in this study. Nineteen patients in the study received a further course of NTG, four of which had initially been treated with NTG. Three of these patients experienced complete healing following the second course of treatment. Longer-term outcome data was later published for patients participating in this study who received 0.2% NTG. It was found that no serious adverse events were noted during the follow-up period (mean 6.2 years). Thirty-two per cent of patients experienced one or more relapses during this time [Demirbag 2005].

Another study assessed the effectiveness of 0.2% NTG ointment (n=22) compared to 10% lidocaine (n=24), EMLA (n=25) or placebo (Vaseline; n=20) in children with anal fissures. The mean patient age was 3 years (range 2.5 months – 15 years). Patients' symptoms were scored, with complete relief given a '2', those without relief given a '0' and incomplete relief a '1'. Fissures were scored 0-2 with deep fissures being scored as 0 and those completely healed as 2 [Sonmez 2002].

Ten days into the 8-week study more patients in the NTG group experienced complete relief of symptoms with complete healing compared to the other arms.

At the end of the study, children showing complete symptom relief and complete healing scores were 91% and 82% in the NTG group versus 76% and 64% in the EMLA group, 42% and 29% in the lidocaine group and 10% and 5% in the placebo group. There was no difference in outcome between NTG and EMLA groups at 8 weeks.

In this study a burning sensation was reported in one NTG-treated patient and two patients in this group experienced hyperemia in the first 3 and 4 days after application. One patient experienced pruritis and one temporary soiling in the NTG group. None of these complications necessitated discontinuation. The authors concluded that a faster response rate was achieved with 0.2% NTG, however, overall there was no difference between NTG or EMLA.

Kenny et al (2001) investigated the effects of 0.2% NTG ointment in 40 children with acute anal fissures in a randomised, placebo controlled, double-blind trial; 31 children completed the trial, 13 in the NTG group and 18 in the placebo group. Parents were instructed to apply a specific amount of ointment, which was applied to the perianal region. The dose was adjusted depending on age and patient response. The primary outcome of this study was time to painless defecation. No differences were observed with respect to time to reach pain free defecation, pain scores and healing rates between the groups over the 16-week study period. However in both groups pain scores had decreased significantly. No serious adverse effects or headaches were observed.

The authors concluded that NTG ointment was ineffective for the treatment of acute anal fissures in children. Explanations offered for these results included effects of telephone follow-up on outcome or alternatively incorrect administration or formulation. Lack of difference could also have been due to fact that acute anal fissures have a high rate of spontaneous healing anyway.

A study by Schiano di Visconte et al (2006) included a number of children with chronic anal fissures. This study compared 0.25% NTG ointment and anal cryothermal dilators with either therapy alone. The age range of patients was 13-44 years and the study involved a total of 48 patients. It was concluded that combined treatment was effective, safe and yielded significantly better results than with individual therapies alone. No specific information is provided with regard to outcomes or complications of the subset of patients who were children in this study, although it is reported that there were no serious side-effects and in no patients treatment had to be withdrawn.

In conclusion, the number of clinical trials is modest, and none of them significant in size, however the overall result is of NTG treatment in anal fissure relieving pain and promoting healing. Apart from a handful of cases of temporary incontinence and headache at the start of treatment, NTG appears well tolerated.

As the pathophysiology of anal fissure and pharmacodynamic response to NTG is similar in adults and children, a clinical study to better understand the safety of topical 0.4% NTG is considered necessary, alongside the demonstrated efficacy of NTG in adults.

Clinical Study

(b) (4)

Endpoints

(b) (4)

Safety

(b) (4)

Clinical Trials

(b) (4)

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PEDIATRIC PAGE

NDA/BLA #: 21-359 Supplement Type (e.g. SE5): Supplement Number:

Stamp Date: July 1, 2004 Action Date: May 1, 2005

HFD-110 Trade and generic names/dosage form: Cellegesic™ (nitroglycerin) Nitroglycerin 0.4% Ointment

Applicant: Cellegy Pharmaceuticals, Inc. Therapeutic Class: 3S New Formulation

Indication(s) previously approved: N/A This is the original NDA for this formulation.

Number of indications for this application(s): 1

Indication #1: Relief of pain associated with chronic anal fissure

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

- Yes: Please proceed to Section A.
No: Please check all that apply: Partial Waiver X Deferred Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver: N/A

- 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
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: N/A

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:

If 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. <1 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Reason(s) for deferral:

Adult studies ready for approval

Other: _____

Date studies are due (mm/dd/yy): Cellegy Pharmaceuticals, Inc. has been requested to submit a general plan and timeline for their pediatric development program to the Division by December 27, 2004.

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: N/A

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

This page was completed by:

{See appended electronic signature page}

Daryl Allis, R.N., M.S.N., F.N.P.
Regulatory Project Manager

cc: NDA 21-359
HFD-960/ Grace Carmouze

(revised 12-22-03)

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

/s/

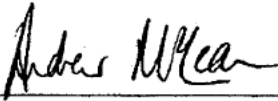
Daryl L. Allis
9/8/04 09:02:43 AM

NDA 21-359

CELLEGESIC™ (nitroglycerin) 0.4% Ointment

DEBARMENT STATEMENT

ProStrakan 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.



Andrew McLean
Company Secretary and
General Counsel



Matthew D' Ambrosio
VP, Legal Affairs and
Chief Compliance Officer

26 May 2009
Date

5/20/09
Date



April 5, 2004

ITEM 16 DEBARMENT STATEMENT

Cellegy Pharmaceuticals, 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.

A handwritten signature in black ink that reads 'David A. Karlin, MD'.

David A. Karlin, MD
Vice President, Clinical Research
Cellegy Pharmaceuticals, Inc.

ITEM 16 DEBARMENT STATEMENT

Cellegy Pharmaceuticals, 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.

Daniel L. Azarnoff, M.D.
Senior Vice President
Clinical and Regulatory Affairs
Cellegy Pharmaceuticals, Inc.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 21359 BLA # N/A	NDA Supplement # N/A BLA STN # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: RECTIV Established/Proper Name: nitroglycerin Dosage Form: ointment 0.4%		Applicant: ProStrakan Agent for Applicant (if applicable): N/A
RPM: Christopher Hilfiger		Division: DAAAP
NDA's: NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)		505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s): NDA 020145 NitroDur Provide a brief explanation of how this product is different from the listed drug. Nitro-Dur is a transdermal nitroglycerin patch If no listed drug, explain. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☐ Other (explain) <u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☒ No changes ☐ Updated Date of check: 6/21/2011 If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.
❖ Actions		
• Proposed action • User Fee Goal Date is <u>06/21/2011</u>		☒ AP ☐ TA ☐ CR
• Previous actions (<i>specify type and date for each action taken</i>)		☐ None 12/23/04 Not Approvable, 7/7/06 Approvable, 3/30/10 CR

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

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics²	
Review priority: ☐ Standard ☒ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rx-to-OTC full switch ☐ Rolling Review ☐ Rx-to-OTC partial switch ☐ Orphan drug designation ☐ Direct-to-OTC NDAs: Subpart H BLAs: Subpart E ☐ Accelerated approval (21 CFR 314.510) ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 314.520) ☐ Restricted distribution (21 CFR 601.42) Subpart I Subpart H ☐ Approval based on animal studies ☐ Approval based on animal studies ☐ Submitted in response to a PMR REMS: ☐ MedGuide ☐ Submitted in response to a PMC ☐ Communication Plan ☐ Submitted in response to a Pediatric Written Request ☐ ETASU ☒ REMS not required Comments:	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

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

❖ Exclusivity	
Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.	☒ No ☐ Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)	☒ No ☐ Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire _____
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).	☐ N/A (no paragraph IV certification) ☒ Verified

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). <i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i> <i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i>	☐ Yes ☒ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist³	6/21/2011
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Not Approvable 12/23/04 Approvable 7/7/06 Complete Response 3/30/2010
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	X
• Example of class labeling, if applicable	

³ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	N/A
• Original applicant-proposed labeling	N/A
• Example of class labeling, if applicable	N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	X
❖ Proprietary Name • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>)	6/16/11 6/14/11
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☐ RPM ☒ DMEPA ☐ DRISK ☒ DDMAC ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	N/A
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) 6/7/11
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	☐ Not a (b)(2) 6/21/11
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC <u>5/25/11</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	☒ Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	9/22/2010

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	☐ No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☐ N/A or no mtg 6/17/2010
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☒ No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None June 21, 2011
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☒ None
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None 5
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	N/A
• Clinical review(s) (<i>indicate date for each review</i>)	5/20/11
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	6/21/11 Summary Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	☒ None requested

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☒ None
Clinical Microbiology Review(s) (indicate date for each review)	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ None
Statistical Team Leader Review(s) (indicate date for each review)	☒ None
Statistical Review(s) (indicate date for each review)	☐ None 5/19/2011
Clinical Pharmacology ☒ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology review(s) (indicate date for each review)	☒ None
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ None
• Supervisory Review(s) (indicate date for each review)	☒ None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None 5/20/2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	☒ None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	☐ None 6/21/2011
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	☐ None 5/19/2011, 6/9/2011
❖ Microbiology Reviews	☐ Not needed 6/14/2011
☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion (<i>indicate review date</i>)(all original applications and all efficacy supplements that could increase the patient population)	5/19/2011
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: 11/5/2009 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

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

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

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

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

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

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

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

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

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

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

/s/

CHRISTOPHER M HILFIGER
06/28/2011

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: Pediatric study of multiple-dose pharmacokinetics study of 0.4% nitroglycerin ointment in subjects ≥ 12 years to < 17 years, in order to determine the appropriate doses for efficacy and safety evaluations.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>1/31/2012</u>
	Study/Trial Completion:	<u>6/30/2013</u>
	Final Report Submission:	<u>12/31/2013</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Studies are ready for approval in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A deferred pharmacokinetic study in pediatric subjects ≥ 12 years to < 17 years.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: Pediatric study of safety and pharmacokinetics in subjects $\geq$ 1 month to < 3 years.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>6/30/2013</u>
	Study/Trial Completion:	<u>6/30/2015</u>
	Final Report Submission:	<u>12/31/2015</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Studies are ready for approval in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A deferred safety and pharmacokinetics study in subjects ≥ 1 month to < 3 years.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
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- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
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PMR/PMC Development Coordinator:

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PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: Pediatric study of safety, efficacy, and pharmacokinetics in subjects ≥ 3 years to <12 years.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>6/30/2013</u>
	Study/Trial Completion:	<u>6/30/2015</u>
	Final Report Submission:	<u>12/31/2015</u>
	Other:	<u>MM/DD/YYYY</u>

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- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A deferred safety, efficacy, and pharmacokinetics study in subjects ≥ 3 years to <12 years.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

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PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: Pediatric study of safety, efficacy, and pharmacokinetics in subjects ≥ 12 years to < 17 years.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>6/30/2013</u>
	Study/Trial Completion:	<u>6/30/2015</u>
	Final Report Submission:	<u>12/31/2015</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

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- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
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3. If the study/clinical trial is a PMR, check the applicable regulation.

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- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A deferred safety, efficacy, and pharmacokinetics study in subjects ≥ 12 years to < 17 years.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
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- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: Multiple-dose pharmacokinetics study of 0.4% nitroglycerin ointment in subjects ≥ 1 month to < 12 years, in order to determine the appropriate doses for efficacy and safety evaluations.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>1/31/2012</u>
	Study/Trial Completion:	<u>6/30/2013</u>
	Final Report Submission:	<u>12/31/2013</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
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2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Multiple-dose pharmacokinetics study of 0.4% nitroglycerin ointment in subjects ≥ 1 month to < 12 years, in order to determine the appropriate doses for efficacy and safety evaluations.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
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- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

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PMR/PMC Development Coordinator:

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(signature line for BLAs)

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

/s/

CHRISTOPHER M HILFIGER
06/21/2011

RIGOBERTO A ROCA
06/21/2011



NDA 021359

**FORMAL DISPUTE RESOLUTION –
Appeal Denied**

ProStrakan, Inc.
Attention: Dalena DeGrezia, M.B.A.
Director, U.S. Regulatory Affairs
1430 U.S. Highway 206, Suite 110
Bedminster, NJ 07921-2652

Dear Ms. DeGrezia:

Reference is made to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for nitroglycerin ointment, 0.4%.

Reference is also made to the complete response (CR) letter of March 30, 2010, to you from Dr. Rigoberto Roca, Division of Anesthesia and Analgesia Products (DAAP, the Division) and to your August 24, 2010, Formal Dispute Resolution Request (FDRR), received August 25, 2010.

Your FDRR asks me to consider whether the circumstances of your application and study REC-C-001 are sufficiently similar to those of Ryzolt (NDA 021745) and study MDT3-005 such that Dr. John Jenkins' January 18, 2008, FDRR response, allowing statistical imputation, referred to by you as the "Jenkins' Analysis," is an appropriate precedent to apply to REC-C-001. You have also asked me to consider, should I determine you have a similar application and issues as those of Ryzolt, that the statistical methods used for MDT3-005 should provide the needed assurance to support the efficacy of the product. In support of this request, you have asked me to consider the three issues listed below.

Issue 1:

Whether FDA considers that the approvability of nitroglycerin ointment, 0.4%, is different from that of Ryzolt because of the difference in the outcome of the primary analysis of their pivotal studies *per se*, although similar outcomes were observed when data were imputed by baseline observation carried forward (BOCF), last observation carried forward (LOCF), and the Jenkins' Analysis, and both sponsors followed FDA's advice on study design, although that advice was different for the two companies.

Issue 2:

Whether the clinical evidence required from the single pivotal trial requested in the July 6, 2006, approvable letter for nitroglycerin ointment, 0.4%, for a new indication is substantially higher than that required from the single pivotal study requested in the September 28, 2006,

approvable letter for Ryzolt, a new non-bioequivalent formulation of tramadol to be used in the already-approved indication.

Issue 3:

Whether a FDRR aimed at resolving the other two issues can be considered prior to any resubmission of the NDA.

I have reviewed the information provided in support of your conclusions and requested action. I have been briefed on the application and the issues in dispute by staff from DAAP and have also consulted with Dr. Robert Temple, Deputy Center Director for Clinical Science, and Dr. Robert O'Neill, Director, Office of Biostatistics, to obtain their counsel on this case. I have also performed a limited literature review regarding the concepts in pathogenesis and treatment of chronic anal fissures.

After careful review and consideration, I conclude that, overall, the issues surrounding use of the Jenkins' Analysis for MDT3-005 are different from those of REC-C-001, and therefore, the Ryzolt action is not an appropriate precedent by which use of the Jenkins' Analysis for nitroglycerin ointment, 0.4%, can be considered. Since I have determined that the issues for your application are different from those of the Ryzolt application, determining whether the statistical methods used in the Ryzolt application should provide assurance of efficacy becomes a moot point. I will summarize the basis for my conclusions below. After summarizing my conclusions, I will comment on two other statistical imputations that may be an option for you if you have the necessary data.

Issues 1 and 2 above are similar and interdependent to some extent in regard to the agency's consideration of Ryzolt; therefore, I will discuss them together. To distill these questions into their most pertinent point, you are asking if you are being held to a different standard than was Ryzolt in our determination of what you perceive to be disparate actions for similar situations. You are implicitly asking if we have violated the concept of a "level playing field" between these applications. In consideration of this question, the 2008 FDRR response letter from Dr. Jenkins to Labopharm Canada, Inc., must be considered in its totality, not in the selected excerpts provided in your FDRR letter. Dr. Jenkins was very clear in his FDRR response that the statistical imputation he suggested should not be employed outside of that particular instance. This point is highlighted in an excerpt from his letter where he states:

"I would emphasize that this conclusion is limited to this particular study, and that I do not think that the use of BOCF is inappropriate in a study that allows for dose titration as a way to minimize drop outs due to lack of efficacy or adverse effects."

You have made the conclusion that the similarities of your situation would allow the Jenkins Analysis to be used. While Dr. Jenkins did opine that his conclusion should be limited to MDT3-005 (the Ryzolt Study), I have closely inspected the record to evaluate whether you have a similar situation. At its heart, your argument revolves around how to handle missing data. In order to conclude that the missing data from REC-C-001 should be handled the same

way as that from the Ryzolt Study, I would first have to conclude that the trial design, previous regulatory history for nitroglycerin ointment, 0.4%, and perhaps the indication should be similar.

To begin this consideration, I first evaluated whether the trial designs were similar. Dr. Jenkins' letter stresses what the specific design limitation in the Ryzolt study was that led to his conclusion:

“I find this particularly true in this specific case since the design of Study MDT3-005 required, apparently at the Division's urging, fixed dosing throughout the study period and did not allow titration of the dose for either lack of efficacy or adverse events.”

Study REC-C-001 did have fixed dosing, however that is because you do not have the option of different dosing strengths allowing for up and down titration to modulate for adverse events. Your trial does not seem to have the same limitation as MDT3-005 where fixed dosing was “urged” despite the flexibility of dose titration. Therefore, your trial design is not comparable and it would not be appropriate to reference the precedent surrounding MDT3-005 as a reason for using the Jenkins' Analysis. Additionally, since the Ryzolt determination, DAAP now allows flexible dosing in clinical trials for drugs that have flexible dosing schedules, which would accommodate the study limitation that Dr. Jenkins identified.

Issue 2 questions the level of clinical evidence necessary, and I agree with you that the discussion should be around the robustness of evidence associated with your program. To discuss this issue, particularly in regard to the Ryzolt application, it is important to review both previous regulatory history and the indications for the two applications. This should also be done to evaluate if there are other differences between the level of evidence your program provides, and the level of evidence the Ryzolt application provided, that would influence the ability to consider the Jenkins' Analysis.

As you noted, both applications were submitted as 505(b)(2) applications. Ryzolt relied for approval on FDA's finding of safety and effectiveness for one or more listed drugs for the same indication as proposed for Ryzolt. In other words, we had previously determined that tramadol, the active ingredient in Ryzolt, had provided “substantial evidence” that it had the purported effect for the purposed indication. Substantial evidence is defined in 505(d) and in our guidance as “. . . evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”¹ This is a high standard and, as stated above, had already been obtained by tramadol. We know for medications such as tramadol what the pharmacological activity (receptor binding) is, we have substantial knowledge of their pharmacology from animal

¹ Guidance for Industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, May 1998.

studies, and we have clinical studies demonstrating efficacy. Tramadol binds the receptors we would associate with pain relief, had nonclinical studies that were consistent with this pharmacologic effect, and had substantial clinical evidence of efficacy in clinical trials. Therefore, we had already determined by a preponderance of evidence that tramadol was effective for the purposed indication. The issue for the Ryzolt application, as you noted, was whether a different pharmacokinetic profile associated with Ryzolt would maintain the already recognized efficacy of tramadol.

Such is not the case for your 505(b)(2) application. Your application relied upon the already established safety of nitroglycerin, but did not reference efficacy, as nitroglycerin has not ever demonstrated the purported effect for the purposed indication. You are seeking a novel use of nitroglycerin that has not as yet been demonstrated by substantial evidence to have the purported effect being sought. Therefore, the 505(b)(2) applications of Ryzolt and nitroglycerin ointment, 0.4%, were similar in that they were both submitted through the 505(b)(2) regulatory pathway, but were different in the scope of what they were relying upon since yours was not relying upon previous demonstrations of efficacy. Therefore, these programs are not equivalent or comparable, and your application must demonstrate substantial evidence of efficacy for the novel indication you are seeking.

The lack of similarity of the scope of information that was being relied upon in addition to the lack of a trial design limitation comparable to that of the Ryzolt program do not support using the Ryzolt precedent of using the Jenkins' Analysis. I therefore disagree with your assertion under Issues 1 and 2 that Ryzolt is an appropriate precedent under which nitroglycerin ointment, 0.4%, should be considered.

For the reasons discussed above, I do not agree that prior to your response to our complete response action, that I should determine that the Jenkins' Analysis would be an appropriate imputation.

Having said the above, I do note your expressed concern that using BOCF would unfairly bias against a treatment where patients may withdraw because of early effective pain relief. This issue deserves more consideration, but must first be put into the context of how DAAP views obtaining a chronic pain indication. The nature of chronic disease is such that it usually does not resolve, but waxes and wanes over time such that any drug therapy should be expected to be effective and tolerated for an extended period of time. DAAP has been very consistent in their advice that, in any efficacy trial, a good score should not be assigned to a subject with a bad outcome (i.e., withdrawal due to an adverse effect of the drug), as this inflates the real efficacy of the drug when used in a chronic setting. This is very logical because if a patient cannot tolerate taking the drug chronically due to adverse events, then the drug really is not effective for use in a chronic setting and should not get any "credit" for an acute (short-term) effect. Drugs of that nature, however, could be candidates for an acute pain indication. Also confounding statistical strategies in chronic pain trials is that there is usually a very high drop-out rate, such that the placebo group at the end of the study is probably not the same group as that which started the study, making any assumptions regarding regression to the mean difficult if not impossible for imputation purposes.

Your application does not seem to be quite the same as what I described above. The “chronic” of chronic anal fissures relates only to their existence (and pain) for duration of greater than six weeks, but most anal fissures ultimately resolve within a few months.^{2,3} This is demonstrated in your application where there was an impressive placebo response, despite a very low drop-out rate (at least in comparison to most chronic pain trials) from the placebo group. This would follow our understanding of chronic anal fissures where the disease does resolve on its own. The low drop-out rate in the placebo group also gives us some assurance that the placebo group completing the trial is similar to the placebo group that began the trial. As such, there are two different ways I would suggest that this can be explored, if you have the available data.

If you have data on the pain level of patients who dropped-out, which was obtained at the actual end of the study (regardless of when they dropped-out), we could use retrieved-dropout methodology as recommended in the recent report on potential imputation strategies⁴ from the National Research Council. Yours would seem to be a fairly straightforward case lending itself quite well to such a strategy in that your trial is of short duration, and you may be able to demonstrate limited use of rescue therapies that would affect the outcome.

A second potential exploration is use of a hybrid LOCF/BOCF imputation. For chronic pain trials, DAAP has been willing to consider using LOCF for drop-outs that were not due to adverse events, while applying BOCF to all other drop-outs. However, given the unique circumstances surrounding your application as outlined above, the division would consider using an LOCF imputation for patients who withdrew because of early effective pain relief, such that their condition did not require further therapy thereby avoiding any potential adverse effects from further drug therapy. I would stress, however, that the burden would be on you to prove that the subject did indeed withdraw because of pain relief, and the results would have to be robust. I also feel that this type of evaluation is probably not as secure as the first option, due to individual interpretation of withdraw reasons, as the first option I outlined above. I emphasize that the considerations I am outlining here for further imputation strategies are unique to your application because of the nature of the disease (high rate of spontaneous resolution), limited placebo drop-out, and limited use of rescue therapy (if proven). I would not anticipate that such strategies would be applicable to other applications.

To summarize, I do not agree that the Ryzolt precedent is applicable to your application. I do feel that there are some unique issues with your application that should receive further evaluation, if you have the data necessary to allow for a robust consideration. To further explore these options or to ask further questions regarding data requirements, please contact DAAP. If you do not have adequate data to pursue the options above and a further trial is necessary, it should be conducted in such a fashion as to obtain the data necessary for the further considerations of evaluation that I outlined above.

² Bhardwaj, R and MC Parker. Modern perspectives in the treatment of chronic anal fissures. *Ann R Coll Surg Engl* 2007; 89:472-478.

³ Utzig, MJ. Concepts in pathogenesis and treatment of chronic anal fissure-A review of the literature. *AJG* 2003; 98:968-974.

⁴ The National Academies Press. *The Prevention and Treatment of Missing Data in Clinical Trials*. <http://www.nap.edu/catalog/12955.html>

If you wish to appeal this decision to the next level, your appeal should be directed to Dr. John Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research. This appeal should be sent again through the Center's Dispute Resolution Project Manager, Ms. Kim Quaintance. Any questions concerning your appeal should be addressed to Ms. Quaintance at (301) 796-0140 or Ms. Amy Bertha at 301-796-1647. Questions regarding next steps with the review division as recommended in this response should be directed to Mr. Christopher Hilfiger, 301-796-4131.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
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/

CURTIS J ROSEBRAUGH
09/22/2010

Reference ID: 2839028

Reference ID: 2969428



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021359

MEETING MINUTES

ProStrakan, Inc.
1430 US Highway 206, Suite 110
Bedminster, NJ 07921-2652

Attention: Dalena DeGrezia, MBA
Director, US Regulatory Affairs

Dear Ms DeGrezia:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for nitroglycerin 0.4% ointment.

We also refer to the meeting between representatives of your firm and the FDA on June 17, 2010. The purpose of the meeting was to discuss our March 30, 2010, complete response letter.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4131.

Sincerely,

{See appended electronic signature page}

Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia and Analgesia and Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:

Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: A
Meeting Category: Post-Action
Meeting Date and Time: June 17, 2010, 11:30 AM
Meeting Location: FDA White Oak Campus
Application Number: NDA 021359
Product Name: nitroglycerin ointment, 0.4%
Indication: relief of pain associated with chronic anal fissures
Sponsor/Applicant Name: ProStrakan, Inc.
Meeting Chair: Robert Shibuya, MD
Meeting Recorder: Christopher Hilfiger

FDA ATTENDEES

Bob A. Rappaport, MD	Division Director
Rigoberta Roca, MD	Deputy Division Director
Robert Shibuya, MD	Clinical Team Leader
Adam Wasserman, PhD	Non-Clinical Supervisor
Newton Woo, PhD	Non-Clinical Reviewer
David Lee, PhD	Clinical Pharmacology Reviewer
Thomas Permutt, PhD	Director, Division of Biometrics 2
Dionne Price, PhD	Statistical Team Leader
Yongman Kim, PhD	Statistical Reviewer
Parinda Jani	Chief, Project Management Staff
Christopher Hilfiger	Regulatory Project Manager

SPONSOR ATTENDEES

Ian Duguid, PhD	Senior VP, Head of Regulatory Affairs
Amanda Cook	Senior Director, Regulatory Affairs
Dalena DeGrazia, MBA	Director, US Regulatory Affairs
Julian Howell, MD	Senior VP, Head of Regulatory Affairs
Kevin Carey	Product Development team Leader

(b) (4)

Background:

New Drug Application (NDA) 021359 was submitted on June 22, 2001, to the Division of Cardio-Renal Drug Products. It was most recently resubmitted to the Division of Anesthesia and Analgesia Products (DAAP). On March 30, 2010, DAAP issued a Complete Response (CR) letter to the sponsor, ProStrakan, for NDA 021359. The sponsor requested an End-of-Review meeting with the Division to discuss the deficiencies in the CR letter. The meeting was granted on May 17, 2010.

The following are the minutes of that meeting. The questions are in *italicized* text. The Divisions preliminary responses are in **bold** text. The discussion, if necessary, is in normal text.

Question 1

Does the Agency agree that the proposed additional analysis presented for the phase III confirmatory study, REC-C-001, provides an acceptable basis for approval upon resubmission?

FDA Response:

The acceptability of the proposed additional analysis can only be determined upon formal review of the resubmission. However, we have some concerns regarding submission of this proposed analysis as a regulatory path forward.

In general, a primary analysis should be pre-specified to alleviate concerns regarding inflation of the type I error. In studies of chronic pain, the Division is concerned that a good score may be assigned to a patient with a bad outcome and therefore advises that the primary analysis should utilize a conservative imputation strategy. This advice was provided to you at the May 22, 2007, meeting. Specifically the Division stated:

“Although acetaminophen is going to be used to prevent headache, it is likely that patients may continue to suffer from headache and still may drop out of the study. It is also likely that patients may drop out due to other adverse events. For this reason, your primary approach for addressing missing data should be more conservative than a last observation carried forward strategy. We recommend use of a method which imputes bad scores to all patients who drop out since these patients will not be successfully treated.”

You chose to conduct an analysis employing a baseline observation carried forward imputation strategy. This approach addressed the Division's concern. Your primary analysis failed. You now propose an additional analysis that apparently reaches statistical significance. Post-hoc selection of a statistical strategy raises multiplicity concerns and is generally not an acceptable practice.

The development of Ryzolt occurred as the science evolved concerning appropriate strategies to handle missing data in chronic pain trials. As such, the statistical question of

interest for the Ryzolt application centered on appropriate sensitivity analyses to demonstrate that the positive results from the primary analysis were not robust to the procedure used to handle missing data. In contrast, your primary analysis failed.

While you cite the Ryzolt approval as a precedent for the use of the proposed analysis, there are several differences between Ryzolt and Nitroglycerin 0.4% Ointment that may be relevant in deciding whether the imputation method used in Study 005 in the Ryzolt development program should apply to your product.

A difference includes, but is not limited to that Ryzolt is an extended-release reformulation of tramadol, a known analgesic moiety. On the other hand, you have proposed to use nitroglycerin, a potent vasodilator approved for angina, hypertension, or congestive heart failure, via a new route of administration and for a new indication, to treat the pain associated with chronic anal fissures.

Discussion:

The sponsor asked whether there was a different regulatory requirement for Cellegesic than for Ryzolt. The Division reiterated the differences between Cellegesic and Ryzolt given above and also noted that Ryzolt was seeking approval for an extended-release (ER) formulation of a drug that was approved as an immediate-release (IR) formulation for the same indication. Cellegesic is seeking an analgesic indication for a drug that is currently approved for use as a cardiac drug, and efficacy needs to be demonstrated since this is a novel indication. Therefore, there are major differences from the regulatory/statistical review of Cellegesic in comparison to Ryzolt.

The sponsor asked whether a dispute resolution was the proper path to address the concerns they have regarding the analysis of the primary endpoint. The Division received a response, from senior FDA management, that since the Division is willing to review a new submission, with a new analysis, that a dispute resolution may not be the proper path forward.

The sponsor stated that Cellegesic is a drug that meets an unmet medical need and that this type of therapy is typically compounded at the pharmacy. The Division responded that, although that may be true, it does not lower the standards of the requirements for an approval. Additionally, approval cannot be based on the fact that the only other treatment is surgical.

The sponsor stated that the previous Complete Response (CR) letter stated that one additional placebo-controlled study would be needed and wanted to know the review outcome if LOCF had been used as it was for Ryzolt. The Division replied that it would likely have responded that LOCF was not an adequate imputation strategy. The Division also added that if a response to the CR letter is submitted then the similarities and differences to the Ryzolt studies should be addressed.

The Division noted that the Jenkins method is not necessarily more conservative than BOCF, so that is not a reason to prefer the Jenkins method over the specified primary analysis.

Question 2a

What additional information in the September 30, 2009, resubmission led to the (non-clinical) deficiency below?

You have not adequately demonstrated that nitroglycerin 0.4% ointment when used at the maximal dosing regimen produces plasma exposures of nitroglycerin and its metabolites which are within the same range of the Reference Listed Drug, Nitro-Dur.

FDA Response:

This is currently under internal discussion. The Division will address this as a post-meeting note.

Question 2b

Does FDA agree that, based on the exposure and clinical safety information presented below, no additional nonclinical information is required in a resubmission and that the information provided is adequate to permit reliance on FDA's findings of safety for Nitro-Dur?

FDA Response:

This is currently under internal discussion. The Division will address this as a post-meeting note.

POST MEETING NOTE:

The submitted information is considered adequate to address the nonclinical deficiency and a release from these nonclinical requirements will be issued in a separate Advice Letter.

Discussion:

No discussion necessary

Question 3

Does FDA agree that the Background information provided adequately responds to the above Deficiency?

FDA Response:

We note that you have updated the NDA in response to the CR letter. These responses will be evaluated by the Agency when the NDA is resubmitted.

Discussion:

No discussion necessary

Question 4

Does FDA agree that the Background information provided adequately responds to the above Deficiency?

FDA Response:

Refer to the response in Question 3.

Discussion:

No discussion necessary

Question 5

Does FDA agree that the Background information provided adequately responds to the above Deficiency?

FDA Response:

Refer to the response in Question 3.

Discussion:

No discussion necessary

Question 6

Does FDA agree that the Background information provided adequately responds to the above Deficiency?

FDA Response:

Refer to the response in Question 3.

Discussion:

No discussion necessary

Question 7

Does FDA agree that the Background information provided adequately responds to the above Deficiency?

FDA Response:

Refer to the response in Question 3.

Discussion:

No discussion necessary

Question 8

Does FDA agree that the Background information provided adequately responds to the above Deficiency?

FDA Response:

Refer to the response in Question 3.

Discussion:

No discussion necessary

Question 9

Does the Agency agree that pediatric studies can be deferred/waived until after the adult indication is approved?

FDA Response:

It is premature to discuss whether a waiver or deferral is appropriate regarding your pediatric studies. We would prefer evidence of efficacy to be demonstrated in adults prior to commencing pediatric studies. However, you should be planning your pediatric studies and developing a scientific argument, supported with data, to support any proposed request. The acceptability of your proposed pediatric program and consideration of any proposal is a review issue. Also, be advised that development of an age-appropriate formulation, possibly a lower strength ointment in this case, may be necessary.

Discussion:

The sponsor asked if a pediatric waiver and deferral could be provided in a new submission. With regard to the waiver, the Division stated that the sponsor should provide more data to support the assertion that younger pediatric patients cannot reliably report the location of pain, thus the assessment of efficacy is difficult. Per the spirit of PREA, pediatric studies should be conducted and should be submitted with the NDA. However, given that efficacy has not yet been demonstrated in adults, the Division will consider deferring pediatric studies until there is evidence of efficacy in adults. A pediatric waiver and deferral may be requested in a new submission but a pediatric plan with adequate support should be in the submission.

Action Items:

1. The proper regulatory pathway to seek approval is to resubmit the application.
2. A pediatric waiver/deferral should be in any new submission with an appropriate pediatric plan.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21359	GI-1	PROSTRAKAN INC	CELLEGESIC NITROGLYCERIN OINTMENT 0.4%
NDA-21359	ORIG-1	PROSTRAKAN INC	CELLEGESIC NITROGLYCERIN OINTMENT 0.4%

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

/s/

CHRISTOPHER M HILFIGER
09/14/2010

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 21359 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: N/A Established/Proper Name: nitroglycerin 0.4% ointment Dosage Form: intra-anal		Applicant: ProStrakan Agent for Applicant (if applicable):
RPM: Christopher Hilfiger		Division: DAAP
NDA's: NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)		505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): NDA 020145 Nitro-Dur Provide a brief explanation of how this product is different from the listed drug. Nitro-Dur is 0.2% nitroglycerin taken orally. ☐ If no listed drug, check box and explain: Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to <u>CDER OND IO</u> for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action. On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity. ☒ No changes ☐ Updated Date of check: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.
❖ Actions		
• Proposed action • User Fee Goal Date is <u>March 31, 2010</u>		☐ AP ☐ TA ☒ CR
• Previous actions (<i>specify type and date for each action taken</i>)		☐ None 12/23/04 Not Approvable, 7/7/06 Approvable
❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received

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

❖ Application Characteristics ²	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rx-to-OTC full switch ☐ Rolling Review ☐ Rx-to-OTC partial switch ☐ Orphan drug designation ☐ Direct-to-OTC NDAs: Subpart H BLAs: Subpart E ☐ Accelerated approval (21 CFR 314.510) ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 314.520) ☐ Restricted distribution (21 CFR 601.42) Subpart I Subpart H ☐ Approval based on animal studies ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☐ Submitted in response to a Pediatric Written Request Comments:	
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	☐ Yes, date
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

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

❖ Exclusivity	
Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).	☒ N/A (no paragraph IV certification) ☐ Verified

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). <i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i> <i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i>	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☐ Included
Documentation of consent/non-consent by officers/employees	☐ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) March 30, 2010
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	N/A
• Original applicant-proposed labeling	Yes
• Example of class labeling, if applicable	N/A

³ Fill in blanks with dates of reviews, letters, etc.
Version: 12/4/09

❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	N/A
• Original applicant-proposed labeling	N/A
• Example of class labeling, if applicable	N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	N/A
❖ Proprietary Name • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>)	12/29/09 12/28/09
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☐ RPM ☒ DMEPA ☐ DRISK ☐ DDMAC ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	N/A
❖ 505(b)(2) Assessment (<i>indicate date</i>)	☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____ • Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	☒ Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	discipline review
❖ Internal memoranda, telecons, etc.	N/A

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 12/4/09

❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	☒ No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☒ No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 3/30/10
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 3/15/10
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	N/A
• Clinical review(s) (<i>indicate date for each review</i>)	3/10/10
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	3/10/10
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☒ None
Biostatistics ☐ None	

⁵ Filing reviews should be filed with the discipline reviews.

Version: 12/4/09

❖ Statistical Division Director Review(s) (indicate date for each review)	☒ None
Statistical Team Leader Review(s) (indicate date for each review)	☒ None
Statistical Review(s) (indicate date for each review)	☐ None 3/2/10
Clinical Pharmacology ☒ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology review(s) (indicate date for each review)	☒ None
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ None
• Supervisory Review(s) (indicate date for each review)	☐ None 3/13/10
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None 3/9/10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	☒ None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	☐ None 1/27/10
❖ Microbiology Reviews	☒ Not needed
☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	1/27/10
☐ Review & FONSI (indicate date of review)	
☐ Review & Environmental Impact Statement (indicate date of each review)	

❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation
☐ BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed

Appendix to Action Package Checklist

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

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

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

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

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

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

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

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

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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-21359

ORIG-1

PROSTRAKAN INC

CELLEGESIC NITROGLYCERIN
OINTMENT 0.4%

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

/s/

CHRISTOPHER M HILFIGER
05/13/2010



NDA 021359

DISCIPLINE REVIEW LETTER

ProStrakan, Inc.
1430 US Highway 206, Suite 110
Bedminster, NJ 07921-2652

Attention: Mary E. Norvitch, PhD
Vice President, US Regulatory Affairs

Dear Dr. Norvitch:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for nitroglycerin 0.4% ointment.

Our reviews of the Clinical, Statistical, and Chemistry, Manufacturing, and Controls (CMC) sections of your submission are complete, and we have identified the following deficiencies:

1. In July of 2006, the Division of Cardiovascular and Renal Products notified you that, prior to approval of this drug, you would have to perform another trial in patients with chronic anal fissure demonstrating improvement in anal pain at the usual level of statistical significance ($p < 0.05$). In response to this deficiency, you conducted and submitted Study REC-C-001, a randomized, double-blind, placebo-controlled, parallel-group study. Our review shows that Study REC-C-001 failed to demonstrate efficacy because the pre-specified, conservative analyses did not yield a statistically significant difference for the primary endpoint.
2. Establish validation criteria for resolution between the impurities in the (b) (4)-0571-LC-P2 analytical method for impurities.
3. ProStrakan Study Report 4, "Preparation of further lab-scale batches of Rectogesic® ointment 0.4%" clearly demonstrates the dependence of the drug product viscosity on the (b) (4). Propose acceptance criteria for (b) (4) viscosity with justification of this acceptance criteria. Your justification should demonstrate the ability to control the drug product viscosity through the proposed expiry period.
4. ProStrakan Study Report 4, "Preparation of further lab-scale batches of Rectogesic® ointment 0.4%" references Report 40002-1135-0509 for information regarding the variance in *in vitro* drug release rates related to formulations using different vendors for excipients. Provide this report and conclusions regarding the components that

affect in vitro release rate. Establish appropriate quality control strategies to control these components.

5. A minimum of three months stability data is required for your registration batches at long-term storage conditions (25°C/60%RH), intermediate storage conditions (30°C/65%RH), and accelerated storage conditions (40°C/75%RH) to bridge your primary (b)(4) and supportive (b)(4) stability data and establish an expiry period. Submit all available stability data for these batches (906493-0, 906494-0, and 906495-0).
 - a. Establish a viscosity specification of NLT (b)(4) cps at release and between (b)(4) cps upon stability.
 - b. Tighten your proposed drug product specifications for the (b)(4) to reflect your current manufacturing process capabilities and stability data.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we 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, call Christopher Hilfiger, Regulatory Project Manager, at (301) 796-4131.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21359	ORIG-1	PROSTRAKAN INC	CELLEGESIC NITROGLYCERIN OINTMENT 0.4%

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/s/

SARA E STRADLEY on behalf of PARINDA JANI
03/15/2010



NDA 021359

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

ProStrakan, Inc.
1430 US Highway 206, Suite 110
Bedminster, NJ 07921-2652

ATTENTION: Mary E. Norvitch, Ph.D.
Vice President, US Regulatory Affairs

Dear Dr. Norvitch:

Please refer to your New Drug Application (NDA) resubmission dated September 30, 2009, received September 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cellegesic (Nitroglycerin) Ointment 0.4%.

We also refer to your September 30, 2009, correspondence, received September 30, 2009, requesting review of your proposed proprietary name, Cellegesic. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

1. Cellegesic is orthographically and phonetically similar to and shares overlapping characteristics with the proprietary name Calagesic. The orthographic similarity of this name pair is attributed to the shared beginning and ending letters ('C and gesic') and the similar appearance of the remaining letters when scripted. These similarities are demonstrated in the scripted samples provided below.

This name pair may sound similar because the beginning letter in Calagesic may be mispronounced with an 'S' sound and both names have four syllables with multiple overlapping letters in a similar sequence. Both products may be prescribed with a signature of 'use as directed' on a medication order or prescribed in terms of the number of tubes or bottles (i.e., one). Consequently, we believe a prescription for "Cellegesic use as directed #1" could be misinterpreted as "Calagesic use as directed #1" or vice versa. Thus, the quantity indicated on a prescription may provide further confirmation for misinterpretation of the prescription. Additionally, both products are available in a single strength thus the strength may not be a distinguishing characteristic since the product strength is not required for dispensing either product. Although Calagesic is available as an 'over-the-counter' (OTC) product, it is not uncommon for practitioners to write prescriptions for 'OTC'

products in a hospital-based practice or to reinforce verbal recommendations to a patient. The orthographic and phonetic similarities of this name pair coupled with product characteristic similarities create the potential for wrong drug medication errors that may occur during transcribing, order entry and dispensing of the drug product.

2. The proposed name Cellegesic is orthographically similar to the name Alagesic. The orthographic similarity of this name pair is attributed to the similar appearance of the beginning letters and the shared ending 'gesic.' These similarities are demonstrated in the scripted samples provided below.



Both are single strength products, indicated for pain relief and overlap with regards to the dose (one inch vs. one tablet). However, if the dose for Cellegesic is written as 1", the abbreviation used for inch may be overlooked and the dose misinterpreted as 1 (representing one tablet). Despite the different frequency of administration an order for "Cellegesic 1" every 12 hours" could be misinterpreted as "Alagesic 1 tablet every 12 hours." The orthographic similarities of this name pair coupled with product characteristic similarities create the potential for wrong drug medication errors that may occur during transcribing, order entry and dispensing of the drug product.

If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, [HTTP://www.fda.gov/cder/guidance/7935dft.pdf](http://www.fda.gov/cder/guidance/7935dft.pdf) and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cheryle Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Christopher Hilfiger.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-21359

ORIG-1

PROSTRAKAN INC

CELLEGESIC NITROGLYCERIN
OINTMENT 0.4%

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

/s/

DENISE P TOYER on behalf of CAROL A HOLQUIST
12/29/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21,359

Proskraton Ltd.
c/o: Skraton Life Sciences, Inc.
1005 Radley Drive
West Chester, PA 18392

Attention: Armand Girard
Senior Development Director

Dear Mr. Girard:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cellegesic (nitroglycerine) Ointment 0.4%.

We also refer to the meeting between representatives of your firm and the FDA on May 22, 2007. The purpose of the meeting was to discuss your response to our July 7, 2006, approvable letter.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Lisa Basham, Regulatory Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Lisa Basham, MS
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

MEETING AGENDA

MEETING DATE: May 22, 2007

TIME: 10:00 AM EST

LOCATION: 10906 New Hampshire Ave. Bldg 22, Room 1309; Silver Spring, MD 20903

APPLICATION (DRUG): NDA 21-359 (Cellestic (nitroglycerine) Ointment 0.4%.

INDICATION: to relieve pain associated with anal fissures.

SPONSOR: Proskratan Ltd.

TYPE OF MEETING: Type A

MEETING CHAIR: Mwango Kashoki, MD, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

MEETING RECORDER: Lisa Basham, Regulatory Project Manager

FDA Attendees	Title
Curtis Rosebraugh, MD	Deputy Director; ODE II
Bob Rappaport, MD	Division Director; Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
Norman Stockbridge, MD	Director; Division of Cardiovascular and Renal Products (DCRP)
Sharon Hertz, MD	Deputy Division Director, DAARP
John Hyde, MD	Acting Deputy Director, DGP
Mwango Kashoki, MD	Clinical Team Leader, DAARP
Suresh Doddapaneni, PhD	Clinical Pharmacology Team Leader for DAARP
Dionne Price, PhD	Statistics Team Leader for DAARP
Robert Levin, MD	Clinical Reviewer, DAARP
Joan Buenconsejo, PhD	Statistics Reviewer for DAARP
Edward Fromm	Chief, Project Management Staff, DCRP
Lisa Basham, MS	Regulatory Project Manager, DAARP
Attendees	Title
Ian Duguid PhD	Head of Regulatory affairs
Gemma Clarke	Director of Clinical Operations
Armand Girard	Senior Development Director
(b) (4)	

Background:

Original Applicant: Cellegy Pharmaceuticals
Original Submission to Division of Cardio-Renal Drug Products: June 22, 2001
Withdrawn: April 25, 2002
Resubmission: June 30, 2004
Not Approvable: December 23, 2004
Type A Meeting: March 28, 2005
Advisory Committee Meeting: April, 2006
Approvable: July 7, 2006
Application transferred to Proskraton Ltd: October 12, 2006
Agency regulatory responsibility transferred to Division of Anesthesia, Analgesia and Rheumatology Products: February 2007

Meeting Minutes

Note: The sponsor's questions are presented below in italicized text, followed by the Agency responses in bolded text. The Agency responses were forwarded to the Sponsor on May 21, 2007. Based upon the Agency's responses, the Sponsor identified, prior to the meeting, the agenda items that required further discussion. All items, however, are listed below, in order, for the record.

Question 1. Can you please confirm that all previous conclusions Division of Cardiology and Renal Products will be recognized? If not, please elaborate.

Agency Response:

We agree with the following conclusions previously reached by the FDA:

- **Studies 98-02-01, 00-02-01, and 03-02-01 failed to show efficacy of Cellegesic as a treatment for pain due to anal fissures.**
- **We agree that an additional study is required to support efficacy of Cellegesic for the proposed indication.**

Discussion: No Discussion necessary.

Question 2. Can you please confirm that the conclusions and recommendations contained within the approval letter are still acceptable?

Agency Response:

See response to Q.1.

We agree with the previous conclusions and with the previous recommendations that the additional efficacy study should:

- Address the potential confounding of background analgesic use.
- Not use the “rate of change in pain” as the primary efficacy endpoint.

Discussion: No discussion necessary.

Question 3. Based on previous clinical studies with Cellegesic 0.4% Ointment (NTG 00-02-01 and CP125 03-02-01) does the FDA concur that the above proposed eligibility criteria are appropriate to measure the product's efficacy in the treatment of chronic anal fissures and address the FDA's concerns about regression to the mean phenomenon?

Agency Response:

Eligibility criteria should describe a patient sample that is reflective of the population of patients that can reasonably be expected to use the product once it is marketed

Your proposed eligibility criteria will select for a population with moderate-severe pain due to chronic anal fissures based on a selection of patients with a VAS score of ≥ 50 mm at screening and on 2 out of 4 days prior to randomization. This may address the previous concerns regarding regression to the mean.

Discussion: No discussion necessary.

Question 4. Does the FDA agree that a demonstration of efficacy in the proposed patient population, together with the efficacy data from the previous clinical studies, will support an indication for the treatment of pain associated with chronic anal fissures, which is unqualified with regards to pain severity?

Agency Response:

Your previous trials suggested that there was no benefit of treatment in patients with mild pain (i.e. low pain scores). If the proposed trial demonstrates evidence of efficacy in the more severely affected patients (i.e. patients with a VAS pain score of

≥ 50 mm), there is still no basis to support evidence of efficacy in patients with mild pain. This may need to be reflected in the labeling but it is premature to say whether that would be through the indication or other sections of the label.

Discussion: No discussion necessary.

Question 5. Does the FDA agree that the proposed primary endpoint as defined above is appropriate to support an indication for the relief of pain associated with chronic anal fissures?

Agency Response:

The proposed primary efficacy endpoint, the change in pain from baseline to a specific time-point, is acceptable to support a pain indication.

Discussion: The sponsor requested clarification on the term “specific time point” and asked whether measurement at 14-18 days is acceptable. Dr. Kashoki responded that 14-18 days is acceptable if that is the appropriate timeframe in which to measure the effect of treatment on pain, as based on the natural course of acute anal fissure pain. The sponsor should provide a rationale for whatever timeframe is chosen for analysis of the primary endpoint. The sponsor stated that they will use 14-18 days of treatment as the “specific time point” for the primary analysis.

An alternative efficacy endpoint to consider is the proportion of treatment responders at the end of treatment (i.e. a responder analysis). We recommend you perform a continuous responder analysis. A responder analysis has the advantage of not requiring any imputation for missing data as subjects who drop-out of the study are considered non-responders.

Discussion: The sponsor stated that they will assess the proportion of treatment responders at the end of treatment as a secondary endpoint, but requested clarification on the Agency’s definition of a continuous responder analysis. Dr. Buenconsejo responded that the continuous responder analysis evaluates the number of patients achieving a percent reduction in pain across the range of cut-off values. The sponsor stated that they plan to present the responder data in two ways: percentage of patients who experience a 10 mm decrease in VAS and the percentage experiencing a 50% reduction in pain. Dr. Price noted that the Division will look at pain reduction across the entire range of cut-off values (i.e. 0% reduction – 100% reduction). She added that it is a clinical decision as to what percentage of pain reduction is clinically relevant. The sponsor asked whether they are required to perform a statistical test on this secondary endpoint. Dr. Price responded that, although encouraged, as a secondary endpoint measure, a formal statistical test is not required.

Dr. Hertz inquired why the sponsor chose a 10 mm decrease in VAS as a clinically relevant reduction in pain. The sponsor responded that this value was based on the available literature for other pain populations. Dr. Hertz stated that the sponsor must provide support for the choice of this 10 mm criterion based on data in an anal fissure population. Dr. Hertz added that the

Division would not consider a 10 mm difference in pain scores between treatment groups clinically relevant without substantial support. Ultimately, this decision is based on the risk:benefit analysis; that is, the balance between treatment effect size and the overall adverse event profile for the drug.

Dr. Hertz continued that the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMPAACT) committee has agreed that there is currently no evidence to support a specific “minimally important difference” between groups with respect to pain; rather, the between-group comparison is context driven. Evaluating a drug’s effect within each individual (responder analysis) may be more meaningful than a comparison of means. The sponsor stated that the continuous responder analysis will be performed as a secondary analysis, and that, once the protocol is operational, they would like to have further discussions with the division regarding the analysis plan. Dr. Rappaport replied that, alternatively, the sponsor may submit the Phase 3 protocol for Special Protocol Assessment (SPA) in order to get agreement on the proposed analyses.

Provide your rationale as to why a trial of 21 days is sufficient to evaluate efficacy of Cellegesic on the pain associated with chronic anal fissures.

Discussion: The sponsor explained that a 21-day trial duration provides a reasonable balance between clinical practice and clinical trial design. A maximal effect of pain is expected after two to three weeks of treatment. Also, patients on placebo may not tolerate a longer period without analgesia. The sponsor will provide additional rationale for the study duration in the submission.

Dr. Kashoki noted the sponsor proposes a relatively short trial for a chronic condition, and asked how the sponsor anticipates that Cellegesic will be used in the target population. The sponsor responded that, although anal fissure pain can be chronic, Cellegesic is intended to treat acute exacerbations of pain. The drug is not intended for chronic or continuous use.

Question 6. Does the FDA agree that a 10 mm decrease in 24-hour average pain intensity (VAS) is clinically significant?

Agency Response:

Clarify your question. Are you asking whether a 10-mm difference between treatment groups in VAS pain scores is clinically significant? Or whether an absolute change of 10-mm (for an individual or a group) is clinically significant? A specific change in pain score that is “clinically significant” has not been established for this indication.

To support a finding of analgesic efficacy, you must demonstrate that the study drug is superior to a comparator in an adequate and well-controlled study. The efficacy is then weighed against the adverse event profile to determine if the benefit outweighs the risk.

We recommend use of the “worst pain in 24 hours” rather than the “average pain” as this is considered a more reliable measure when assessing pain by recall.

Discussion:

Dr. Hertz clarified that the clinical significance of the difference in mean pain scores between treatment groups would be a review issue based on the overall risk/benefit ratio.

Regarding the Division’s recommendation to measure the “worst pain in 24 hours,” the sponsor explained that patients with anal fissures have a chronic background pain that is exacerbated by bowel movements; therefore, “worst pain” becomes a marker for bowel movement, which in turn reflects fiber and fluid intake. Thus, the “worst pain” is a noisy measure and the “average pain” is preferred because it takes into account patients’ persistent pain, irrespective of whether or not they have a bowel movement that day. Dr. Hertz agreed that, with this condition, average pain would be a more appropriate measure. She recommended that the sponsor collect “worst pain in 24 hours” as a secondary measure, to provide further information about the effects of Cellegesic on pain.

Question 7. Does the FDA agree with the proposed methodology and the handling of dropouts?

Agency Response:

The primary analysis using ANCOVA model, with treatment, country, and gender as factors, and baseline VAS pain as a covariate, is acceptable.

The primary patient population (i.e. intent-to-treat) should include all randomized patients who took at least one dose of study medication.

Discussion: Dr. Buenconsejo clarified that the ITT population should include all randomized patients who received at least one dose of study medication. For patients who only have a baseline score, a baseline observation carried forward imputation strategy should be used for missing data.

For patients who drop out of the study, clarify how you would handle the post-discontinuation data and the imputed data in the primary analysis.

Discussion: For patients who drop out of the study before 18 days, the sponsor proposed assigning zero change from baseline in the VAS pain score. Dr. Buenconsejo agreed with this approach to imputing missing data.

Although acetaminophen is going to be used to prevent headache, it is likely that patients may continue to suffer from headache and still may drop out of the study. It is also likely that patients may drop out due to other adverse events. For this reason, your primary approach for addressing missing data should be more conservative than a last observation carried forward strategy. We recommend use

of a method which imputes bad scores to all patients who drop out since these patients will not be successfully treated.

Discussion: The sponsor expressed concern about assigning bad scores to patients who drop out due to headache when the patients, otherwise believe that they received benefit from the drug, as reflected by the patient global assessment score. Dr. Kashoki explained that because analgesics provide symptomatic relief, they are beneficial only during the period of time that they are taken. Thus, if a patient drops out of a trial, for whatever reason, they have not benefited from the drug, and should receive a bad score.

The sponsor asked whether use of scores from the patient global assessment could be factored into the imputed score, since some patient may discontinue due to an adverse event but otherwise report that the benefit of treatment exceeded the adverse effects. Dr. Hertz replied that the patient global assessment typically do not reflect assessment of a clear construct. Patients respond to global questions about treatment effect based on their expectations and previous experiences. It would not be possible to impute pain scores based on favorable or unfavorable global assessments since there is no way to understand discrepancies between pain scores, global assessments, and decisions to discontinue study participation.

Dr. Hertz suggested that the sponsor consider capturing information about patients' willingness to reinstate Cellegesic treatment following discontinuation for intolerable effects such as headache. Dr. Rappaport added that it would be interesting to look at individual patients' patterns of pain. It is best to develop a definition of responder based on the global assessment and pain score and then test the definition with prior data, so that it can be validated, but it may be too late to do that at this stage of development.

Specify what other sensitivity analyses you proposed to perform when there are appreciable numbers of patient dropouts.

Discussion: The sponsor stated that they would use a "zero change" imputation strategy for the primary efficacy analysis, and agreed to perform additional sensitivity analyses and to examine the pattern of pain scores for the patients who withdraw from the study. The sponsor asked whether details of the Statistical Analysis Plan (SAP) could be finalized at a later date. Dr. Hertz agreed, but noted that if the protocol is submitted as a SPA, it would need to contain a complete analysis plan. Dr. Price recommended that, if the sponsor does not submit the protocol under a SPA, the protocol should contain as detailed a statistical plan as possible.

See also the response to Q. 5.

Question 8. Does the FDA agree that this is an acceptable proportion of US patients?

Agency Response:

Yes. You must ensure that the data provided from the foreign sites is of sufficient quality to support the NDA.

Discussion: No discussion necessary.

Question 9. Does the FDA agree that the use of acetaminophen in this study is appropriate?

Agency Response:

Provide your rationale for why pre-treatment of nitroglycerin-induced headache with acetaminophen is expected to be effective in reducing the occurrence of intensity of this type of headache.

If use of acetaminophen as a pretreatment does reduce the incidence or severity of headaches due to Cellegesic, we would need to use the headache data from prior trials to inform the risk:benefit assessment of this product.

Discussion: See discussion under question 10.

Question 10. Additionally, would the mandated use of acetaminophen in this study require its use to be included in the labeling?

Agency Response:

If acetaminophen use is a cardinal feature of the protocol, then it may need to be described in the product label. However, we have reservations regarding the use of acetaminophen as standard pre-treatment for Cellegesic. There is a risk of hepatotoxicity associated with the use of acetaminophen. If it is necessary to pretreat patients with acetaminophen in order to successfully treat them with Cellegesic, this will need to be considered in the overall risk:benefit assessment for this product.

Discussion: The sponsor acknowledged the Division's concerns regarding acetaminophen (APAP), including the potential labeling implications, and the hepatotoxicity concerns. Based on the mechanism of action of APAP and on the efficacy data from previous studies, they do not believe that APAP has any effect on anal fissure pain. They would prefer to administer APAP on a prn basis (i.e. as needed for pain). However, earlier Agency concerns about the potential confounding effects of APAP on efficacy resulted in the Agency's advice to either give APAP to everyone, or ban its use entirely during the studies.

Dr. Hertz suggested the sponsor consider performing the pain assessments prior to use of rescue which can improve retention without interfering with the pain assessments. However, the sponsor would need to explore how this can be done, given that the primary efficacy measure is the average pain over 24 hours.

From a regulatory standpoint, in order to remove the concern regarding the potential effect of APAP on anal fissure pain, a separate clinical trial could be performed that demonstrates the absence of an effect. The data would need to be convincing that there is no effect, and "no effect" would need to be clearly defined.

The sponsor noted that the proposed APAP administration is within the maximum recommended over-the-counter dosing (OTC) dosing range and should, therefore, not cause hepatotoxicity. Also, in clinical practice, APAP is often used to treat nitroglycerin-induced headache. Dr. Hertz responded that there is great concern at present about APAP and hepatotoxicity, even with OTC dosing. Therefore, pretreatment with APAP would need to be considered in the overall risk/benefit analysis, and may also result in inclusion of APAP use in the product label. A compelling argument would be required as to why co-use with APAP should not be described in the label if that is how the study was performed. Dr. Rappaport added that there is currently no clear regulatory answer or pathway to deal with this concern. In response to the sponsor's question, Dr. Rappaport stated that the APAP concern was a review matter, not a hold issue.

Dr. Hertz suggested a three-arm study with an APAP arm added to the trial, to show that there is no effect of APAP on anal pain. The sponsor pointed out that patients are aware that APAP does not relieve their pain, so it would be difficult to get patients to enroll in such a study. The sponsor said that they will comb through their data to date and consider the discussed approaches. Dr. Hertz stated that the sponsor should provide a well-thought-out rationale for any proposal on this issue.

Question 11. Does the FDA agree that our approach to global assessment is acceptable?

Agency Response:

Yes, it is an acceptable approach.

Discussion: No discussion necessary.

Question 12. Does the FDA agree that our approach is appropriate to determine the effect of Cellegesic on vital signs?

Agency Response:

The proposed monitoring approach is inadequate. Pre- and post-treatment vital signs should be obtained on all patients, if not during all clinic visits, at least during

the initial visits. Vital signs should be measured at 5 and 10 minutes post-dosing, in addition to 30 minutes and 1 hour post-dose.

All patients should be assessed for orthostatic hypotension during all clinic visits.

ECGs should be obtained on all patients at screening and at the end of the study.

Discussion: The sponsor confirmed that vital signs will be collected pre- and post-dose on days 0 and 7, orthostatic hypotension assessed at all visits, and ECGs performed pre-and post-study.

Question 13. Does the FDA agree with the proposed methodology for the interim analysis?

Agency Response:

The proposed methodology appears acceptable. However, we have strong reservations about your proposed use of an interim analysis. In particular, based on the extremely limited evidence of efficacy, it seems unwise to risk obtaining less efficacy information by reducing the power of the study by early termination prior to full enrollment. It is already difficult to maintain the study blind based on the adverse event profile of Celegesic compared to placebo and there is risk that this could influence interpretation of the interim data. We strongly encourage you to perform the study without the interim analysis if the intent of the interim analysis is to discontinue the study early based on evidence of efficacy.

Discussion: The sponsor agreed with the Agency's recommendation to remove the interim analysis.

Question 14. If the study is stopped early because of superiority, please confirm the results of the interim analysis will be adequate to demonstrate substantial evidence of safety and efficacy?

Agency Response:

It is impossible to confirm that the results of the interim analysis will be adequate to demonstrate evidence of efficacy at this time. We will only be able to make a determination of evidence of efficacy in the setting of a review of all of the data available. As noted, we do not recommend stopping the study early based on early evidence of superiority given the difficulties in demonstrating efficacy in prior studies.

Discussion: No discussion necessary.

Additional Discussion Point: The Sponsor asked if the results of the proposed study, in combination with previous data, would be acceptable to support the filing of a New Drug Application. The Division stated that it would accept the previous reviewing division's commitment for a single additional study.

KEY DISCUSSION POINTS:

1. The integral of pain over 14-18 days of treatment is acceptable for use as the "specific time-point" for the primary analysis.
2. The cumulative proportion of treatment responders at the end of treatment will be evaluated as a secondary endpoint and a continuous responder analysis will be performed.
3. Clinical significance of mean difference between treatment groups will be a review issue based on the overall risk/benefit ratio.
4. The sponsor will provide their rationale for use of average pain as an endpoint as opposed to worst pain.
5. The sponsor will use a "zero change" imputation strategy for missing data and evaluate patterns of pain for individual patients.
6. All randomized patients who receive at least one dose of study drug will be included in the ITT population.
7. The sponsor's proposal to use APAP is acceptable with the caveat that labeling and hepatotoxicity issues will be considered during review.
8. Vital signs will be collected pre- and post-dose on days 0 and 7, orthostatic hypotension will be assessed at all visits, and ECGs will be performed pre- and post-study.
9. The interim analysis will be removed from the protocol.
10. The proposed study, in combination with previous trials, will be sufficient to support the filing of a New Drug Application.

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this page is the manifestation of the electronic signature.**

/s/

Lisa Basham
6/13/2007 02:54:31 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-359		Supplement Number N/A
Drug: Cellegesic™ (nitroglycerin) 0.4% Ointment		Applicant: Cellegy Pharmaceuticals, Inc.
RPM: Mr. John David	HFD- 110	Phone # 301-796-1059
Application Type: ☐ 505(b)(1) ☒ 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct. ☒ Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 20-145 Nitro-Dur®	
❖ Application Classifications:		
• Review priority: Class I Resubmission following Not Approvable letter		☐ Standard ☐ Priority
• Chem class (NDAs only)		3; New Formulation
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		June 15, 2005
❖ Special programs (indicate all that apply)		☒ None ☐ Subpart H ☐ 21 CFR 314.510 (accelerated approval) ☐ 21 CFR 314.520 (restricted distribution) ☐ Fast Track ☐ Rolling Review ☐ CMA Pilot 1 ☐ CMA Pilot 2
❖ User Fee Information		
• User Fee		☒ Paid UF ID number 4141 Resubmission; Fee paid June 2001
• User Fee waiver		☐ Small business ☐ Public health ☐ Barrier-to-Innovation ☐ Other (specify)
• User Fee exception		☐ Orphan designation ☐ No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ☐ Other (specify)
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		☐ Yes ☒ No

Version: 6/16/2004

This application is on the AIP	() Yes (X) No
Exception for review (Center Director's memo)	N/A
OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) (X) Verified
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	21 CFR 314.50(i)(1) () (ii) () (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	N/A
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i> [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)). <i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i> (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? <i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i> <i>If "No," continue with question (3).</i> (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	() N/A (no paragraph IV certification) (X) Verified
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)). <i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i> (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? <i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i> <i>If "No," continue with question (3).</i> (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	(X) Yes () No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? <i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i> <i>If "No," continue with question (3).</i> (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	() Yes () No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	() Yes () No

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

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

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

Yes No

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

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	N/A
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.	☐ Yes, Application # _____ ☐ No N/A
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	June 15, 2006

General Information	
❖ Actions	
• Proposed action	☐ AP ☐ TA ☒ AE ☐ NA
• Previous actions (specify type and date for each action taken)	Not Approvable; December 23, 2004
• Status of advertising (approvals only) N/A	☐ Materials requested in AP letter ☐ Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	☐ Yes ☒ Not applicable
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ 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)	N/A
• Most recent applicant-proposed labeling	N/A
• Original applicant-proposed labeling	Yes
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	Yes
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Yes
❖ Memoranda and Telecons	Yes
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	Type A: March 28, 2005
❖ Advisory Committee Meeting	
• Date of Meeting	April 25, 2006
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	N/A
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	May 26, 2005
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	N/A
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	1 st Review Cycle; in DFS
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	N/A
❖ Biopharmaceutical review(s) (indicate date for each review)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	N/A
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	N/A
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: N/A () Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested () Not yet requested N/A
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

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

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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this page is the manifestation of the electronic signature.**

/s/

John David
7/27/2006 07:51:54 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Hilton Washington DC/North Hotel, Gaithersburg, Maryland

Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee meeting on April 25, 2006.

The committee discussed new drug application (NDA) 21-359 Cellegesic™ (nitroglycerin [NTG] ointment), 0.4% intra-anal, Cellegy Pharmaceuticals, Inc., for the proposed indication of relief of pain associated with anal fissures

These summary minutes for the April 25, 2006 meeting of the Cardiovascular and Renal Drugs Advisory Committee were approved on May 3, 2006.

I certify that I attended the April 25, 2006 meeting of the Cardiovascular and Renal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

//S//
Cathy A. Groupe, R.N., B.S.N.
Executive Secretary

//S//
William R. Hiatt, M.D.
(Committee Chair)

FINAL SUMMARY MINUTES
Cardiovascular and Renal Drugs Advisory Committee Meeting
April 25, 2006

A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at <http://www.fda.gov/ohrms/dockets/ac/cder06.html#CardiovascularRenal>

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

Attendance:
Cardiovascular and Renal Drugs Advisory Committee

Members Present (voting):
David L. DeMets, Ph.D.
Steven D. Findlay, M.P.H. (Consumer Representative)
John M. Flack, M.D., M.P.H.
Robert A. Harrington, M.D., F.A.C.C.
William R. Hiatt (Committee Chair)
Frederick J. Kaskel M.D., Ph.D.
Michael A. Lincoff, M.D.
Thomas G. Pickering, M.D, D.Phil.
Ronald J. Portman, M.D.
John R. Teerlink, M.D.
Lynn Warner-Stevenson, M.D.

Special Government Employee Consultants (voting):
Walter A. Koltun, M.D. (participating via teleconference)

(Non-Voting) Participants:
George S. Goldstein, M.D. (Industry Representative)

Cardio-Renal Advisory Committee Members Absent:
John F. Neylan, MD (Industry Representative)

FDA Participants:
Robert Temple, M.D.
Norman Stockbridge, M.D., Ph.D.

Executive Secretary:
Cathy A. Groupe, R.N., B.S.N.

Open Public Hearing Speakers

None

The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on April 25, 2006, at the Hilton Washington DC/North Hotel, Gaithersburg, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the sponsor and the FDA. The meeting was called to order by William R. Hiatt, M.D. (Committee chair); the conflict of interest statement was read into the record by Cathy Groupe, RN, BSN (Executive Secretary). There were approximately 50 persons in attendance. There were no speakers for the Open Public Hearing sessions.

Issue: New drug application (NDA) 21-359 Cellegesic™ (nitroglycerin [NTG] ointment), 0.4% intra-anal, Cellegy Pharmaceuticals, Inc., for the proposed indication of relief of pain associated with anal fissures

The agenda was as follows:

Call to Order and Introductions	William R. Hiatt, M.D. Committee Chair Cardiovascular and Renal Drugs Advisory Committee
Conflict of Interest Statement	LCDR Cathy Groupe, B.S.N. Executive Secretary Cardiovascular and Renal Drugs Advisory Committee
Introduction/Background	Norman Stockbridge, M.D. Director - Division of Cardiovascular and Renal Drug Products FDA/CDER

Sponsor Presentation – Cellegy Pharmaceuticals, Inc.

Overview of Phase 1 and	Daniel L. Azarnoff, M.D., F.A.C.P.

FINAL SUMMARY MINUTES
Cardiovascular and Renal Drugs Advisory Committee Meeting
April 25, 2006

Phase 3 Studies	President, D.L. Azarnoff Associates Professor of Medicine University of Kansas Medical Center
Pathophysiology of Anal Fissures and Clinical Aspects Of Diagnosis and Treatment	Michael E. Abel, M.D., F.A.C.S., F.A.S.C.S. Assistant Clinical Professor of Surgery University of California at San Francisco Medical School
Overview of Studies And Regulatory History	Daniel L. Azarnoff, M.D., F.A.C.P
Safety	Daniel L. Azarnoff, M.D., F.A.C.P.
Statistical Methods and Analyses	Robert D. Gibbons, Ph.D. Professor of Biostatistics and Director Center for Health Statistics University of Illinois at Chicago
Risk Benefit Profile	Jonathan Lund, B.M.B.S., D.M., F.R.C.S. Associate Professor School of Medical and Surgical Sciences University of Nottingham
Summary and Conclusions	Thomas Q. Garvey, III, M.D., F.A.C.P. President Garvey Associates, Inc

Questions from the Committee

Break

Lunch

FDA PRESENTATION:

Effect Size – Can the Effect Size Be Too Small?

Robert J. Temple
Director - Office of Drug Evaluation I (ODEI)
FDA/CDER

Committee Discussion

Questions to the Committee

Questions to the Committee:

The Committee is asked to opine on Cellegesic (0.4% nitroglycerin ointment) for the symptomatic treatment of pain associated with anal fissures. Study 98-02-01 (or Study 1) was conducted to assess the effect of nitroglycerin ointment on healing of anal fissures. This study was not successful, but the sponsor perceived a favorable trend on pain relief. Study 00-02-01 (Study 2) was undertaken to confirm this finding on pain relief. The second trial was positive ($p < 0.05$) by the sponsor's analysis, but this analysis was not fully specified prospectively and it differed from the hypothesis-generating analysis of Study 1. By the Study 1 analysis, Study 2 was not statistically significant, and the Agency deemed the two studies an inadequate basis for approval. Study 03-02-01 (Study 3) was expected by the sponsor and by the Division to provide the necessary assurance of effectiveness.

By the prospective analysis, the sponsor asserts that the p-value in Study 3 was 0.0498, but the sponsor believes a more appropriate analysis gives $p=0.0243$. The review team believes that the prospective analysis gives $p=0.12$. The differences all result from handling of patients with missing data because of early withdrawal for headache.

There are two issues. The Advisory Committee is being asked first whether it finds the data compelling that there is an effect on anal fissure pain. The second issue is whether the apparent effect size warrants approval. At the end, then, the Committee will be asked to choose among 3 outcomes:

- Approval = The evidence is compelling, and the effect size is either large enough to matter or it is irrelevant.
- Approvable = The evidence is not compelling, and the effect size is either potentially large enough to matter or it is irrelevant.
- Not Approvable = Effect size matters and the available data rule out an effect large enough to support approval.

1. The sponsor believes Study 2 should have been considered persuasive, because the post-hoc inclusion of a quadratic term in the regression analysis was justified (backgrounder pages 11 and 28).

1.1. What is the interpretation of the linear term in an analysis with a quadratic model?

- *The committee was satisfied that the quadratic model was appropriate and reasonable, citing the non-linear nature of the data. However the use of this model was a post hoc decision.*
- *Others commented the benefit of the short-term gain in avoiding surgery should be taken into consideration*

(See transcripts of detailed discussion)

1.2. Was the quadratic model the proper analysis for the purpose of decision-making? Please vote.

YES: 7 NO: 5

(See transcripts for detailed discussion)

2. Study 3 called for a Last Observation Carried Forward analysis of pain data from subjects who discontinued “due to headache”. The sponsor interpreted this to mean treatment-related headache, leading to the previously cited $p=0.0498$. Various alternative analyses are summarized below (from Dr. Hung’s review of July 2004):

	Conditions	P-value
1	LOCF for withdrawal for drug-related headache	0.0498
2	Add all available data for 1 subject	0.0843
3	LOCF for withdrawal for any headache	0.12
4	LOCF for any withdrawal	0.0943-0.15
5	No imputation	0.0489
6	No imputation and no post-withdrawal data	0.0309

2.1. Is the analysis based on “drug-related” headache a reasonable interpretation of the protocol? Is it reasonable to expect that the determination of drug-relatedness would be unambiguous?

- *There was general agreement among most of the committee that the analysis based on ‘drug-related’ headache was not reasonable; most commented that it should have been defined as ‘any headache’.*

2.2. The sponsor’s backgrounder comments extensively on the use of LOCF with a mixed-effects model. Should LOCF have been included in the analysis?

- *Many committee members commented that a mixed model is the best model when data are missing at random. However since drug-induced headaches accounted for many drop outs, the management of missing data remained an issue.*
- *Some committee members abstained from making a conclusion, commenting lack of knowledge of the difference between the two models.*

2.3. A few subjects had data following discontinuation. Should their post-discontinuation data have been included in the primary analysis?

- *Most of the committee thought that data should have been included in the primary analysis while a few felt it should not be included.*
- 2.4. Subjects enrolled with one kind of pain and discontinued with a different pain. Was LOCF conservative enough?
- *Clarification of the question was added, stating 'Should we have used LOCF'?*
 - *The majority of the committee did think LOCF was appropriate [PLEASE CLARIFY THIS, I THOUGHT WE DID APPROVE INCLUSION OF MISSING DATA IN THE ANALYSIS]*
- (See transcripts for detailed discussion)*
3. The review team questioned whether concomitant analgesic use could have contributed to differences in the groups. The sponsor has argued that the results are not confounded by analgesic use.
- 3.1. Do you agree that the results are not confounded? If so, cite the analysis you find compelling.
- *The committee raised concern about acetaminophen compliance in study patients*
 - *Some of the committee members agreed that they were not convinced that analgesics were not confounders while others commented that it is difficult to know. Most agreed, though, that this was not a concern.*
- 3.2. What magnitude of effect of analgesics can be excluded?
- *Most of the committee agreed that not much of the magnitude of effect can be excluded*
- (See transcripts for detailed discussion)*

4. Taking all three studies into consideration, do you find the data compelling that there is an effect of nitroglycerin ointment on the pain of anal fissures? Please vote.

YES: 9 NO: 3

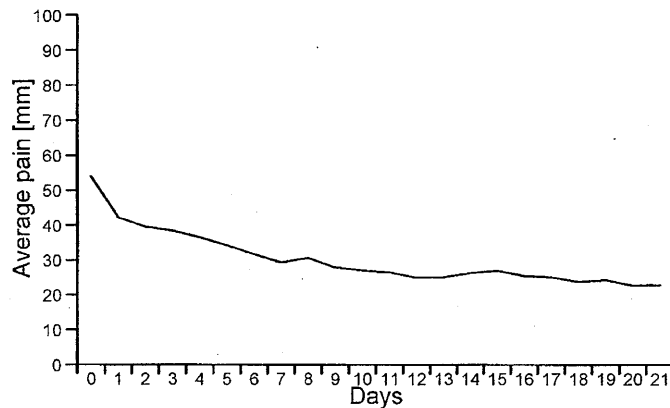
(See transcripts for detailed discussion)

5. Nitroglycerin ointment administered intra-anally is systemically absorbed—mean bioavailability 50% with wide variability even in a small PK study (range 8-99%). At the extreme, the proposed dose thus delivers 1.7 mg of nitroglycerin in the first hour, substantially higher than the usual anti-anginal dose. Dosing was erratic in the trials—apparently as much as 4-fold overdosing based on an FDA site audit. Tachycardia and dizziness were reported in two patients in the small clinical trials, but vital signs were not measured at peak after the first visit. Are there safety issues with the use of nitroglycerin ointment to treat anal fissures?

Comments from the committee included:

- *Dizziness was cited as a potential safety issues, where presyncope or syncope may be a factor.*
 - *That there may be safety issues but that these issues may not be a significant factor*
 - *We do not know how this drug will interact in patients on other blood pressure medications; this population should be excluded until further data is available*
6. Independent of the need to show net benefit exceeding risk, which of the following factors, if any, influence whether or not the size of a treatment effect matters for regulatory decision-making?
- Benefit is a reduction in major clinical outcomes
 - Benefit is an improvement in functional status
 - Benefit is an improvement in global patient assessment
 - Benefit is an isolated symptom
- Comments from the committee included:*
- *Many committee members agreed the magnitude of the effect for all factors is important, while others cite that while these factors matter, effect size is difficult to quantify.*
 - *Rapid reduction in pain (symptom) was cited as a significant factor in determining the size of a treatment effect*
- (See transcripts for detailed discussion)*

7. Does treatment of anal fissure pain belong to a class of indication for which the effect size matters? If not, proceed directly to question 10.
 - *While a few of the committee members did not think the effect size matters, a majority of the committee agreed that it does matter*
(See transcripts for detailed discussion)
8. The instrument used to assess effectiveness in these trials was a 100-mm visual analog scale. In study 3, mean response in the placebo group is shown in the figure below (no imputation).

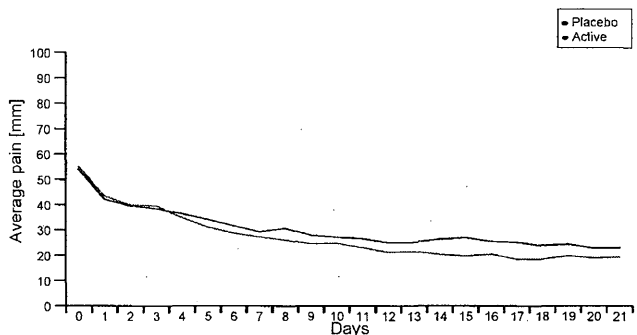


Page 19 of the sponsor's briefing package shows a similar figure for Studies 1 and 2 combined.

- 8.1. Since subjects had to have some minimum pain score to get into the study, some of this effect is regression to the mean. Can you estimate how much is regression to the mean and how much is the natural history of the disease?
 - *Committee members commented on the difficulty in determining this, while most agreed that the first part of the curve (day 1), is clearly regression to the mean. Estimates included 10-20 days as the natural history of the disease.*
(See transcripts for detailed discussion)

The figure below shows the mean effect in the placebo and active treatment groups in Study 3 (again with no imputation).

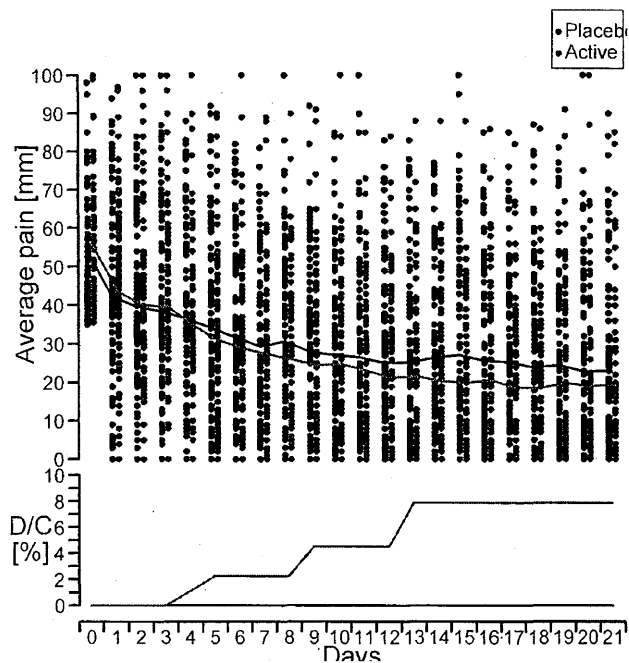
FINAL SUMMARY MINUTES
 Cardiovascular and Renal Drugs Advisory Committee Meeting
 April 25, 2006



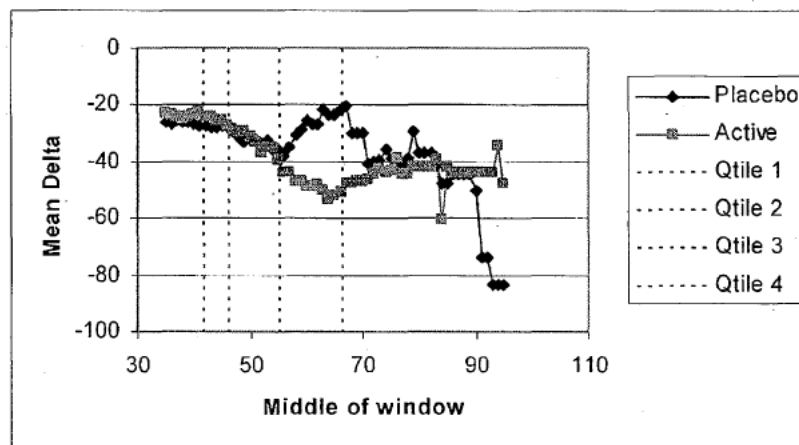
8.2. How large is the nominal treatment effect (active minus placebo)? How does it compare with the effect seen in the placebo group?

- The effect size varies over time
- Many committee members estimate a 1/3 nominal treatment effect compared with placebo
- Others comment that there is clearly an effect but it is unclear if they improved a lot versus a little

The figure below shifts the placebo and active group curves slightly and adds all of the observed data. Along the bottom now runs the discontinuation rate in the two groups.



- 8.3. A patient, regardless of Cellegesic, is, generally, going to feel better over time. Is a patient apt to perceive the contribution Cellegesic makes?
- Some committee members agreed that, yes, the patient is apt to perceive the contribution Cellegesic, adding that while it is a small effect, it is a real one. Still others commented that what individual patients perceive is unclear.
 - Other committee members commented that it is difficult, from the figure above, to make a determination.
- (See transcripts for detailed discussion)
9. The sponsor presents an analysis (backgrounder pages 39-42) to show that the effect of Cellegesic is larger in upper quintiles of baseline pain score. Compare this with an analysis performed using a 10-mm-wide moving bin, shown in the figure below.



Overall, are the data compelling that patients with worse pain at baseline respond better to Cellegesic?

- The committee cited that this is a hypothesis generating plot for a follow-up study
 - A majority of the committee agree that, yes, the data are compelling that patients with worse pain at baseline response better to Cellegesic; others commented that this was suggestive but not compelling
- (See transcript for detailed discussion)

10. What is the appropriate regulatory action for Cellegesic? Please vote for one of the following options:

- Approval
- Approvable pending another study of effectiveness
- Not approvable

APPROVAL: 6

APPROVABLE PENDING ANOTHER STUDY OF EFFECTIVENESS: 6

NOT APPROVABLE: 0

- Those committee members who voted for 'Approval' cited that additional studies may not provide beneficial data as well as adding that the drug is currently being used extensively off-label, which would challenge adequate enrollment in a new trial

The committee adjourned at approximately 5:50 P.M.

(See transcript for detailed discussion)



NDA 21-359

DISCIPLINE REVIEW LETTER

Cellegy Pharmaceuticals, Inc.
Attention: Daniel L. Azarnoff, M.D, F.A.C.P.
1000 Marina Blvd., Suite 300
Brisbane, CA 94005

Dear Dr. Azarnoff:

Please refer to your new drug application (NDA) originally submitted June 22, 2001, withdrawn April 25, 2002, and resubmitted June 30, 2004 and April 14, 2005, received April 15, 2005, under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cellegesic™ (nitroglycerin) 0.4% Ointment.

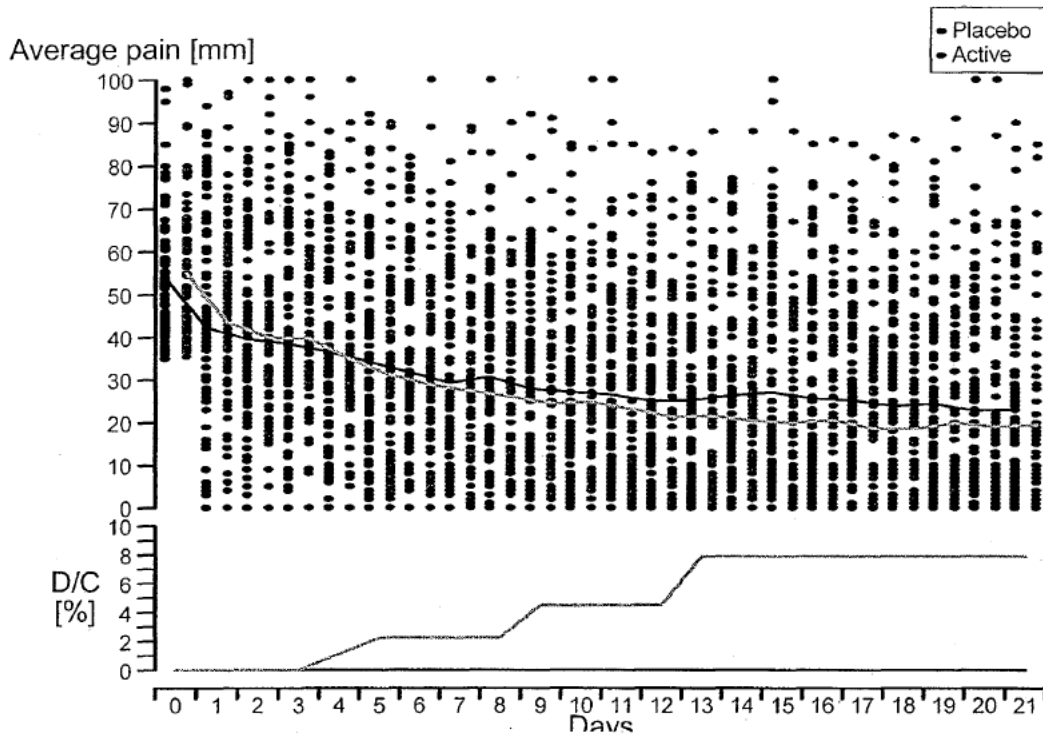
We acknowledge receipt of your submissions dated January 27 (2), February 28, and April 14, 2005. The April 14, 2005 submission constituted a complete response to our December 23, 2004 action letter.

Our reviews of your submission are complete, and we have identified the following deficiencies:

Division Director's Comments

Your submission of 14 April 2005 addresses some issues relating to the robustness of the statistical analysis of study CP125-03 and the consistency of all three studies. The fundamental problem remains the one cited first in the first action letter—the treatment effect is quite small. The result is that a fairly big study has only marginal power, and then the details of how one handles special circumstances—like withdrawals or concomitant pain medications—matter inordinately. However, if the robustness of the result was the fundamental issue, you would have received an “Approvable” action, and not a “Not Approvable” one.

This problem is illustrated in the figure below:

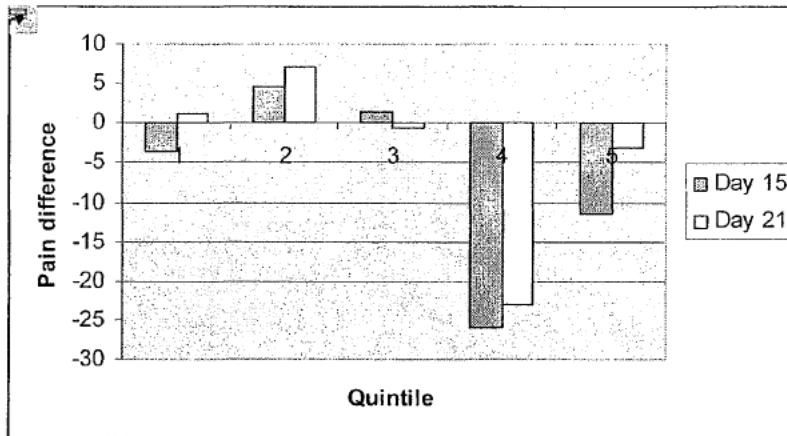


This figure is based on the CP125 dataset and it shows all of the pain measurements (and no imputations). The lines in the upper part connect the means by day for the two treatment groups. For patients who remained in the study to 3 weeks, the difference pain level is a few mm on the VAS, an effect that is about 10% of the placebo effect and about 10% of the standard deviation on any day. The result may mean that, in a large enough sample, there will be less pain on nitroglycerin ointment than on placebo, but no individual has any chance to perceive the benefit of treatment over placebo. This is not a satisfactory result for a symptomatic treatment.

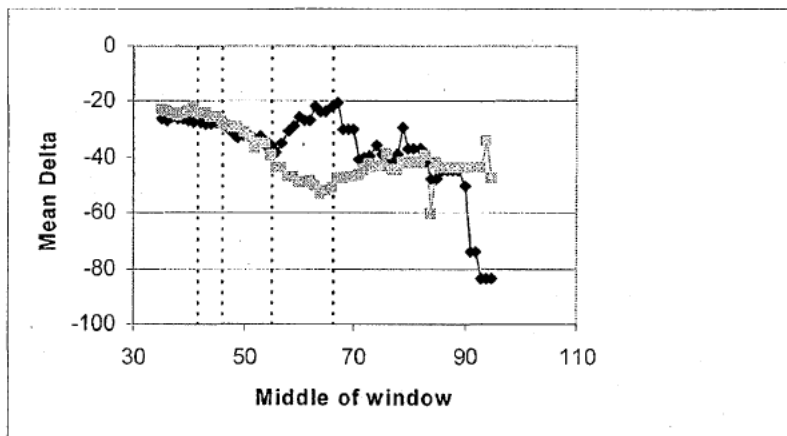
We remain concerned that this meager effect is an overestimation. The above simple analysis takes no account of the difference in rate of discontinuation (lower part of the figure above) and no account of the difference in acetaminophen use.

You conclude that acetaminophen use was not a significant contributor to the observed differential response between the treatment groups. However, this analysis does not show what magnitude of the effect of acetaminophen has been ruled out.

You analyze patients in the highest strata of pain at baseline and conclude that the magnitude of treatment effect (change from baseline and placebo) is substantially larger than the magnitude of effect in the study overall. The combined analysis of all three studies has this pattern, and perhaps study 3 alone does, too.



The data in this figure are derived from Table 3 in your complete response submission. However, if one takes the underlying data from the CP125, again doing no imputation, and looks at the change from baseline to day 21 using a 10-mm-wide moving window approach, one gets the following:



While you would be welcome to explore the effectiveness of nitroglycerin ointment in a population with a higher baseline pain score, we do not believe that study 3 provides a strong basis for such a study.

Medical

The submission includes data and reports for three clinical efficacy studies in support of this indication. These studies do not provide substantial evidence of efficacy of NTG ointment for this indication. The first failed on its primary endpoint of improving anal fissure healing but the sponsor interpreted secondary analyses as suggesting that NTG ointment relieves pain. The second study had a primary endpoint of improvement in the rate of decrease of pain over a 56-day period but this endpoint showed statistically significant improvement only with an analysis not clearly prespecified in the protocol. By the analysis prespecified in the protocol the result was not statistically significant. The third study had a primary endpoint of improvement in the rate of decrease of pain over a 21-day period that showed a nominally statistically significant result ($p < 0.0498$) when the sponsor analyzed the data not carrying forward the last observation for some patients who discontinued due to headache as the protocol specified. When the

data are analyzed by the protocol-specified methodology, the p value is 0.12. This study has additional weaknesses of a tiny treatment effect (about 3 mm on a 100 mm visual analog pain scale), excessive dropouts in the NTG group, possible confounding by partial unblinding due to NTG-induced headaches and use of acetaminophen for them, and reasonable improvement demonstrated only in one country.

The size of the safety database in this application is small (only 167 patients completing the regimen proposed to be marketed) and monitoring for adverse effects was not optimal. While there are no safety findings that alone preclude approval, the uncertainty about safety contributes to the negative risk vs. benefit assessment.

Brief Overview of Clinical Program

Collegesic NTG ointment is a formulation of nitroglycerin (NTG) 0.4% (w/w) in a white petrolatum and lanolin base compatible with a USP monograph. It is intended for use as a self-administered treatment to be applied intra-anally at the site of a chronic anal fissure for relief of pain. The proposed dosing is 375 mg every 12 hours. Because NTG is a drug in widespread use for many years in approved sublingual and topical formulations, the sponsor did not perform preclinical studies, but relied upon literature reports of such studies.

The three clinical efficacy trials reported in the application were randomized, double-blind, placebo-controlled, parallel group studies. The first study was conducted in the US, while the other two were international studies. All studies enrolled adults with anal fissure, defined as a linear tear of the anoderm distal to the dentate line. Anal fistulas and fissures secondary to recent anal surgery were excluded. For the first study, anal pain was not required, but anal pain was mandatory for the second two studies. For the third study, a confirmed sentinel pile was also mandatory. While the first study had a primary endpoint of fissure healing at 28 days, average anal pain was recorded daily by the patient on a 100 mm visual analog scale (VAS) in all three studies.

The first study, NTG 98-02-01, enrolled 360 patients and tested regimens of 0.1%, 0.2%, and 0.4% BID and TID versus placebo. The second study, NTG 00-02-01, enrolled 229 patients and tested regimens of 0.2% and 0.4% BID versus placebo. The third study, CP125 03-02-01 compared 0.4% BID to placebo. I summarize the results of these efficacy studies in the next section.

The application also includes the results of one small pharmacokinetic study in six normal subjects comparing single dose intra-anal NTG, repeated dose intra-anal NTG, and IV NTG. This study estimated a mean bioavailability of intra-anal NTG of about 50% with a wide variability (standard deviation of 30%). These numbers suggest that intra-anal NTG may lead to systemic adverse effects (as the clinical efficacy studies confirmed), and that the occurrence of these adverse effects could be erratic.

Efficacy

Study NTG 98-02-01 did not show a favorable effect of NTG ointment for the primary endpoint, fissure healing. Healing was observed in 49% of placebo, 40% of 0.1% NTG, 33% of 0.2% NTG, and 44% of 0.4% NTG patients (pooling the BID and TID regimens). Using a mixed effects regression model that was not pre-specified the sponsor found a significant effect of 0.4% NTG ointment on average daily pain, but no significant differences for the two lower doses. The significance of the results depends upon the precise definition of the regression model, e.g., changing the definition of the residuals eliminates the statistical significance of the 0.4% NTG effect. The results are also not internally consistent, e.g., 0.4% NTG BID appears better than TID but for lower dosages TID is better. These results did justify doing a second study targeting pain relief.

Study NTG 00-02-01 targeted improving the rate of change in daily average pain through 56 days evaluated by a mixed-effects regression model as was done for the first study. By a regression model also incorporating center and quadratic components (not pre-specified and not done for the first study) the

sponsor found a significant treatment by linear time interaction for the 0.4% NTG group ($p=0.005$), but not for the 0.2% NTG group. However, besides the issue of lack of pre-specification, the treatment by linear time interaction is not the rate of change. Evaluating the rate of change by the linear mixed-effects regression model without the center and quadratic components produces statistically insignificant results ($p = 0.85$ for 0.2% NTG and $p = 0.24$ for 0.4% NTG).

You had submitted the first two studies in an initial NDA submission. When informed about the Division's interpretation of the two studies, you withdrew the NDA. The Division and sponsor discussed the performance of a third study to show convincing results. You incorporated most, but not all, of the Division's recommendations into the third study.

Study CP125 03-02-01 targeted improving the rate of change in daily average pain through 21 days evaluated by a mixed-effects regression model without the quadratic component. NTG patients discontinuing the study due to headache were to have their last observation carried forward (LOCF). For this endpoint, you reported a p-value of <0.0498 . The mean changes calculated are -24.9 for placebo and -28.1 for NTG, a difference of 3.2 mm favoring NTG on a 100 mm visual analog scale. However, your handling of some patients' data for its primary analysis is not consistent with the protocol specification. We note that you did not use the LOCF for two patients who discontinued due to headache. For the analysis that matches the description of the primary analysis in the protocol, the p-value is 0.12.

The evidence for efficacy of NTG ointment from this study is even weaker than the p-value of 0.12 implies. The effect size estimate, even with the sponsor's liberal analysis, is small. This study is plagued by a high dropout rate only in the NTG ointment arm: 11 (12%) randomized patients discontinued before day 21, and 9 (9.5%) have incomplete data through day 21. The Division made known in advance that a high dropout rate would make this study unintermittible. My confidence in any suggestion of a benefit for NTG ointment is weakened further by the potential for partial unblinding because of headaches with NTG ointment and confounding by acetaminophen use and because reasonable improvement with NTG ointment was demonstrated only in one country.

You also performed analyses combining data from the 0.4% NTG ointment groups of the three studies. The fundamental problem with these analyses is that they were not prespecified. They are subject to unstated selection criteria that may be used to produce positive results and misleadingly high p-values. The great variation in p-values depending upon how the analyses are done is shown by the discussions above of the three individual study results. For the combined analyses, this variability is also present. If the 0.2% BID groups are included, then 0.2% NTG appears as worse than placebo as 0.4% appears better. There is no evidence for a dose-response relationship that would help to confirm efficacy.

All three of these studies fail to show statistical significance for their primary endpoint analyses. The estimated magnitude of a benefit, if any, of NTG in relieving pain of anal fissure is small, e.g., a mean improvement of about 3 mm on a 100 mm visual analog scale at day 21 even with the sponsor's liberal analysis and is confounded by many issues regarding analyses not prespecified, data exclusions, excessive dropouts with NTG, acetaminophen use, and benefit limited to one country. These studies do not provide substantial evidence of efficacy of NTG ointment in relief of pain associated with chronic anal fissure.

Safety

The size of the safety database in this application is small. Only 475 patients received any dose of NTG ointment, 206 patients received any dose of NTG ointment 0.4% BID (the regimen proposed to be marketed), and 167 of these patients completed a treatment period of 56-days. Of the latter, only 19 patients were age 65 or older. The most frequent reason for withdrawal was adverse event in 20 (10%, typically headache), but another 13 (6%) withdrew for "patient choice".

No deaths occurred during the clinical trials. Ten patients experienced serious adverse events (SAEs) during the trials, four placebo, two 0.4% NTG BID, and four other NTG dosing. There is no pattern to the SAEs.

Overall, 45 NTG (22 0.4% BID patients) and 7 placebo patients discontinued treatment due to an adverse event (AE). Headache was the most common AE leading to discontinuation in 29 NTG patients (about 8% of the 0.4% BID patients) compared to 2 (about 1%) of the placebo patients. For any NTG use, vomiting was the cause for discontinuation in 4 patients, nausea in 3 patients, and burning sensation, tachycardia, dizziness, and vertigo in 2 patients.

The most frequent AEs were headache (38% placebo and 67% NTG 0.4% BID) and nausea (1% placebo and 6% NTG). In the third study alone, headache was reported by 67% of placebo and 86% of NTG patients, indicating a low threshold for reporting. More NTG patients reported severe headaches (34% vs. 3.4%), took medication for it (48% vs. 28%), and had longer symptoms (mean 8 hours vs. 4.3 hours). The second most common AE in this study was upper abdominal pain, reported by 11% of placebo patients and 18% of NTG patients.

There were no reports of hypotension or low blood pressure. However, there were withdrawals for tachycardia, bradycardia, and dizziness. Vital signs are not reported for these patients. Vital signs were typically measured pre-dose (except 10-20 minutes post-dose at day 1 in the first two studies) and showed no pattern.

In addition to the small size of the safety database, there are two other limitations worth noting: (1) Vital signs were not obtained at the time of estimated peak drug levels after chronic exposure. It would be helpful to know how much blood pressure is affected and the variability of it. (2) The case report forms provided minimal information on the adverse events. For example, tachycardia and bradycardia were reported for several patients, but no information is provided on heart rate, heart rhythm, or blood pressure.

The potential or lack of potential of NTG ointment for causing dangerous cardiovascular AEs is not well explored in the limited exposure in the Cellegesic development program with limited information on blood pressure changes and AEs. While the available data do not confirm that NTG ointment is a dangerous drug, they also do not provide sufficient reassurance that it is safe.

Dosing Regimen and Administration

The dosing regimen was selected based on the first study examining a range of doses (0.1, 0.2, and 0.4%) and BID and TID dosing, and the second study testing 0.2 and 0.4% BID. While the regimen proposed to be marketed was selected based on the suggestion of best pain relief, the evidence was weak and the efficacy of 0.4% BID was not supported by the third study. The rate of headaches with the 0.4% BID regimen suggests that higher doses would not be acceptable. We believe that the failure of this development program lies not with an inappropriate regimen, but with inadequate efficacy of NTG for this condition.

You propose marketing Cellegesic (nitroglycerin) 0.4% ointment in both a metered dose canister and in a tube. The canister has a metered dose-dispensing pump for dispensing of 375 mg of ointment; the tube's carton has a line for measuring a 375 mg dose. In the pharmacokinetic study, bioavailability was highly variable (8% to 99%) and overdosing was common at the sites audited by DSI (possibly to fourfold). For average bioavailability numbers, the 375 mg dose of 0.4% NTG ointment delivers about 0.4 mg/hour, comparable to rates of systemic NTG delivery from NTG patches for angina. For the highest extremes of bioavailability, the proposed dose delivers about 1.7 mg in the first hour, substantially higher than the usual antianginal dosages. We are concerned that a delivery rate of 1.7 mg or higher in the first hour could be dangerous in vulnerable patients and that the size of the safety database is too small to exclude such problems.

Drug-Drug Interactions

You did not perform any drug-drug interaction studies but relied upon the published literature regarding NTG. This approach is acceptable for pharmacokinetic interaction studies.

Special Populations

You did not study any special populations except that both genders were adequately represented in the clinical trials. Blacks and the elderly are sparsely represented in the clinical studies. Children were not studied, and the Division granted a deferral of pediatric studies in a letter dated August 26, 2004, because the drug would be ready for approval in adults before studies in children would be completed.

NTG use has not been associated with varying efficacy or safety issues in either gender or specific ethnic groups. The elderly, who have a higher burden of chronic disease such as hypertension, coronary heart disease, and heart failure are a population for whom adverse effects of NTG are more problematic.

Statistical

In Table 5 provided by Dr. Tom Marciniak – Medical Reviewer, 195 (not 193) patients were randomized. Of them, two NTG patients were ineligible. The sponsor’s randomized set has 100 subjects in the placebo group and 93 in the NTG groups. Of the 193 patients, two subjects per treatment group from the Russian site and one lost to follow up and one not dosed (both are in the NTG group) were excluded from the sponsor’s analysis set. The sponsor’s analysis data set contains 98 placebo subjects and 89 NTG subjects. Of the 89 NTG subjects, one (subject 037-367) discontinued due to subject choice, two (008-052, 037-159) discontinued due to headache and their post discontinuation data were imputed by the LOCF described above, and another two (005-070, 037-358) discontinued due to headache, but they were censored at the time of discontinuation. In addition, two NTG subjects, 037-374 and 037-380, had post discontinuation data. Subject 037-380 had post discontinuation data and also the imputed data using the specified LOCF algorithm; the two data are quite different.

Table 5: Medical Reviewer’s Subject Disposition and Data Completeness to Day 21

Category	Placebo		NTG	
	N	Subject ID	N	Subject ID
Randomized	100		95	
Ineligible	0		-2	008-049, 026-326
Sponsor’s “randomized”	100		93	
Excluded Russian site	-2	043-149, 043-151	-2	043-150, 043-152
Lost to follow-up	0		-1	008-167
Subject choice D/C, not dosed	0		-1	017-054
Sponsor’s analysis set	98		89	
Subject choice D/C, sponsor censored	0		-1	037-367
Headache D/C, sponsor LOCF	0		-2	008-052, 037-159
Headache D/C, sponsor censored	0		-2	005-070, 037-358
Data complete to day 21	98		84	
*Headache D/C, sponsor LOCF	0		-1	037-380
*More pain D/C, all data used	0		-1	037-374
Sponsor’s “completed day 21”	98		82	

* Diary to day 21; D/C = discontinued study drug

Table 6 presents a number of the reviewer's analyses performed because of differential dropouts between the two treatment groups. Note that subject 037-380 discontinued the drug due to drug-related headache but had post-discontinuation data. In the sponsor's primary analysis (p=0.0498), the actual observed data for this subject were replaced by the LOCF imputed data. The actual observed data and the LOCF imputed data are very different. It was said in Attachment #7 (page 9) of the 9/21/2004 document that from a statistical perspective it is preferable to use the actual observed data following study discontinuation, when available, as opposed to simply assuming that the missing data are consistent with the data prior to study discontinuation. If the actual observed data were used for this subject, then the p-value would be 0.0843. Moreover, protocol-defined primary analysis that imputes missing post discontinuation data due to headache (not just drug-related headache) gives p = 0.12, not statistically significant. Depending on how the post discontinuation data of the dropouts are handled, the p-value changes substantially from analysis to analysis, ranging from 0.0309 to 0.15.

Table 6. Primary efficacy endpoint – rate of change and mean change from baseline in average VAS score for pain intensity due to anal fissure at Day 21 (the sponsor's ITT patient population) [Source: Reviewer's analysis]

	Placebo (N=98)	NTG (N=89)	NTG - placebo in slope ($\pm$ SE)	p-value
Sponsor's primary analysis: LOCF for discontinuation only due to drug-related headache ¹	-31.0	-34.6	-0.29 $\pm$ 0.15	0.0498
Same as ¹ , except using all available data for subject 037-380 ²	-31.0	-34.5	-0.26 $\pm$ 0.15	0.0843
LOCF for discontinuation due to all reasons, except using all available data for 037-374 ³	-31.0	-34.6	-0.25 $\pm$ 0.15	0.0943
Same as ³ , except also using all available data for subject 037-380 ⁴	-31.0	-34.5	-0.22 $\pm$ 0.15	0.15
Protocol-defined primary analysis: LOCF for discontinuation due to headache ⁵	-31.0	-34.5	-0.24 $\pm$ 0.15	0.12
Use all available data and do not impute missing data ⁶	-31.0	-34.6	-0.30 $\pm$ 0.15	0.0489
Delete post discontinuation data and do not impute missing data ⁷	-31.0	-34.4	-0.32 $\pm$ 0.15	0.0309

¹ sponsor's primary analysis: impute post discontinuation data only for 008-052, 037-159, 037-380, censor at discontinuation for 005-070, 037-358, 037-367, use all available data for 037-374

² impute post discontinuation data only for 008-052, 037-159, censor at discontinuation for 005-070, 037-358, 037-367, use all available data for 037-374, 037-380

³ impute post discontinuation data for 008-052, 037-159, 037-380, 005-070, 037-358, 037-367, use all available data for 037-374

⁴ impute post discontinuation data for 008-052, 037-159, 005-070, 037-358, 037-367, use all available data for 037-374, 037-380

⁵ impute post discontinuation data for 008-052, 037-159, 005-070, 037-358, censor at discontinuation for 037-367, use all available data for 037-374, 037-380

⁶ use all available data for 037-380 and 037-374, do not impute missing data for remaining five dropouts

⁷ delete post discontinuation data, do not impute

The NTG appeared to relieve pain faster than the placebo; see Figure 1 for completers plus the two dropouts (037-374, 037-380) who had complete data up to Day 21. If there were no bias, the p-value of this analysis (completers plus these two dropouts) would be 0.059. However, the results of this analysis and any of the analyses presented in Table 6 may have been substantially biased in favor of NTG for the following reasons. The placebo group did not have a dropout. All seven dropouts are in the NTG group; their average pain intensity profiles are plotted in Figure 2. In six of the seven dropouts, the average pain intensity seemed to trend toward worsening one or more days before discontinuation. For subjects 037-374 and 037-380 who had post discontinuation data after discontinuation, only subject 037-374 had pain score trending flat after discontinuation. The pain scores of subject 037-380 got worse fast for at least a week immediately after discontinuation at Day 9. These response profiles imply that the proposed LOCF method even with variability added to imputed pain scores might still overestimate the slope of the average pain change for these subjects. That is, the p-values as given in Table 6 are likely to be smaller than what the unbiased p-value should be. In addition, the NTG group has four randomized subjects who were declared ineligible, lost to follow up or not dosed. These four patients had no data and were excluded from analysis. It is certainly not possible to guess how these subjects would have performed had they been in the study. This uncertainty adds difficulty to the analysis and the interpretation of the treatment comparisons. In sum, this study fails to provide sufficient evidence in support of the hypothesis that NTG reduces pain due to anal fissure during the first 21 days of the treatment.

Figure 1. Mean change from baseline in average pain intensity in the completers and the two dropouts (037-374 and 0374-380) who had post discontinuation data up to Day 21

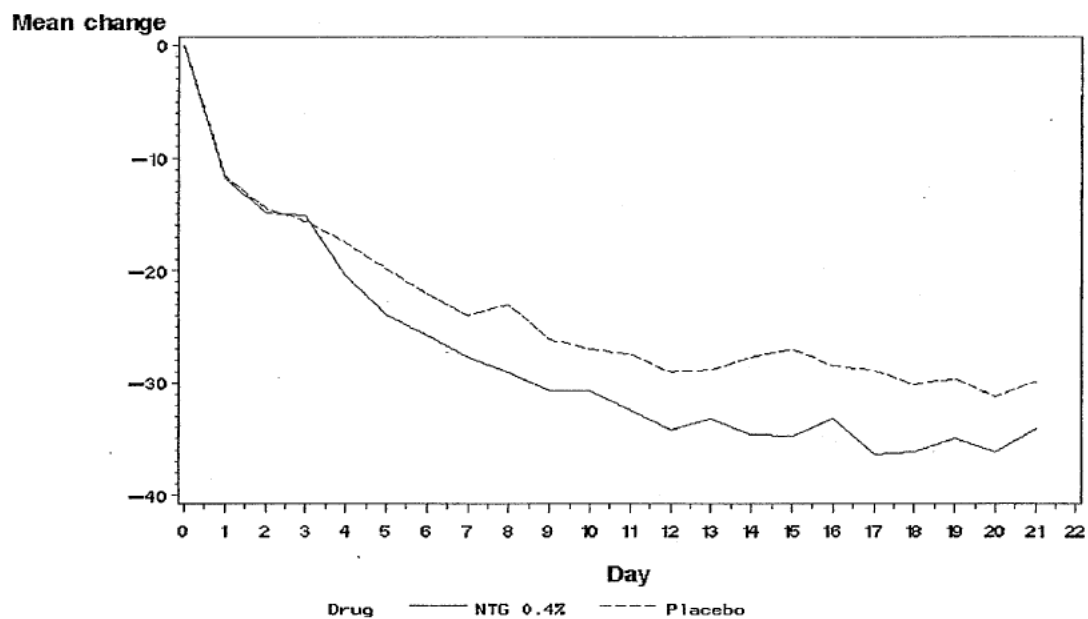


Figure 2. 24-hour Average Pain Intensity of Dropouts up to Day 21
[subject 037-374 discontinued on Day 5 and subject 037-380 discontinued on Day 9]

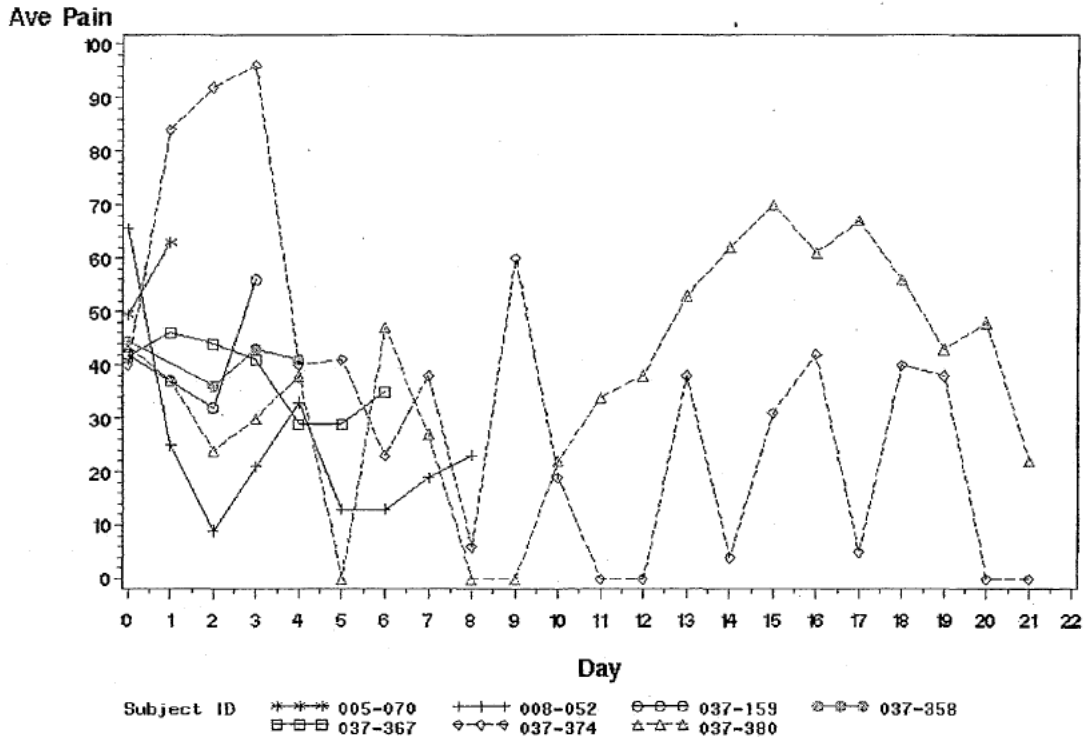


Table 7 provides the mean change from baseline in average pain intensity score at Day 21 by site, based on the protocol-specified primary analysis (i.e., impute post discontinuation data for 008-052, 037-159, 005-070, 037-358, censor at discontinuation for 037-367, use all available data for 037-374, 037-380 and completers). Of the 17 sites, as compared to placebo, NTG was numerically substantially worse in 6 sites, not much different in 3 sites (difference is less than one), substantially better in 8 sites. This by-site result adds little to support NTG on potential pain relief effect.

Table 7. Mean change from baseline in average pain intensity score at Day 21 by site – protocol specified primary analysis (i.e., impute post discontinuation data for 008-052, 037-159, 005-070, 037-358, censor at discontinuation for 037-367, use all available data for 037-374, 037-380 and completers)

[Source: Reviewer's analysis]

Site #	Placebo (N=98)		NTG (N=89)	
	n	Mean change	n	Mean change
24	10	-31.5	10	-44.4
26	4	-42.5	3	-38.2
32	6	-30.7	6	-48.4

33	6	-41.6	6	-27.8
35	8	-26.6	7	-26.4
37	10	-26.4	10	-10.9
41	8	-16.2	8	-35.1
42	4	-44.6	4	-43.9
44	4	-28.8	4	-38.6
100	6	-19.3	3	-39.3
101	6	-28.2	3	-34.6
102	4	-26.0	4	-43.9
103	4	-36.8	4	-27.3
104	3	-49.0	4	-39.5
105	4	-30.5	3	-25.0
106	5	-32.2	4	-32.5
107	6	-41.7	6	-47.6

Clinical Pharmacology

Comments for the NDA submitted June 30, 2004

The clinical pharmacology of nitroglycerin has been previously described since it is commercially available in various dosage forms and has been used for many years for the treatment of angina. Nitroglycerin vasodilates both arterial and venous systems. When dosed intra-anally it is proposed to heal anal fissures and relieve the pain.

You have conducted one pharmacokinetic study. This study characterizes the absorption of nitroglycerin when given by the intra-anal route. The assay validation information was missing from the original NDA. Additionally, you did not provide drug release information about the ointment.

Comments to the Sponsor

You were requested to submit the assay validation information for the pharmacokinetic study.

You may want to consider conducting an in-vitro study to characterize the drug release of Cellegesic.

Comments to the Medical Officer

NDA 21-359 is acceptable from a clinical pharmacology and biopharmaceutics perspective. The to-be-marketed formulation contains a ^(b)₍₄₎% overage of nitroglycerin, whereas the clinical formulation contained a ^(b)₍₄₎% overage. The difference in overage is acceptable according to the USP monograph.

Clinical Pharmacology Memo (Resubmission NDA 21-359 April 14, 2005)

On March 12, 2002, the Office of Clinical Pharmacology and Biopharmaceutics reviewed NDA 21-359, Cellegesic, for the treatment of chronic anal fissures and found that the clinical pharmacology and biopharmaceutics section was acceptable for approval provided that the assay validation be found acceptable. The current resubmission contains acceptable assay information.

No new PK data are contained in the current submission. You resubmitted study NTG 98-02-02 entitled, "A study to determine the pharmacokinetics and bioavailability of Anogesic 0.2 % (0.75 mg) applied to the anal canal". This study number was changed to 98-03-02 in the current submission; however, it is the same study.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we 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 Mr. Daryl Allis, Regulatory Project Manager, at (301) 796-1034.

Sincerely,

{See appended electronic signature page}

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

**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
1/31/2006 12:38:50 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-359

Cellegy Pharmaceuticals, Inc.
Attention: Dr. Daniel L. Azarnoff, M.D., F.A.C.P.
1000 Marina Blvd., Suite 300
Brisbane, CA 94005

Dear Dr. Azarnoff:

We acknowledge receipt on April 15, 2005 of your April 14, 2005 resubmission to your new drug application for Cellegesic (nitroglycerin) 0.4% Ointment.

We consider this a complete, class 1 response to our December 23, 2004 action letter. Therefore, the user fee goal date is June 15, 2005.

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 reference the deferral granted on August 26, 2004 for the pediatric study requirement for this application.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation 1
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/

Edward Fromm
4/29/05 03:22:53 PM

Minutes of a Meeting

Meeting Date: March 28, 2005 (Sponsor's request; February 23, 2005 not acceptable)
Application: NDA 21-359 Cellegesic (nitroglycerin) 0.4% Ointment
Sponsor: Cellegy Pharmaceuticals, Inc.

Type of Meeting: A
Classification: Stalled Development

Meeting Request: January 31, 2005
Sponsor Notified: February 3, 2005 (Telephone conversation)
Confirmation Faxed: February 3, 2005
Briefing Package Date: January 31 & March, 2005
Meeting Chair: Robert Temple, M.D.
Meeting Recorder: Daryl Allis

Attendees:

Division of Cardio-Renal Drug Products

Robert Temple, M.D.	Director, Office of Drug Evaluation I
Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Acting Deputy Director, Medical Officer, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
James Hung, Ph.D.	Team Leader, Statistics, HFD-710
John David, R.N., M.S.H.R.M.	Regulatory Health Project Manager, HFD-110
Daryl Allis, R.N., M.S., F.N.P.	Regulatory Health Project Manager, HFD-110

Cellegy Pharmaceuticals, Inc.

Richard Williams	Chairman and Chief Executive Officer
Daniel Azarnoff, M.D.	Consultant, Clinical/Regulatory Affairs
David Karlin, M.D.	Vice President, Clinical Research

(b) (4)

Background

Cellegy Pharmaceuticals, Inc (Cellegy) requested this Type A meeting to gain further clarity of the cited deficiencies listed in our action letter dated December 23, 2004 and to determine whether the information provided in Attachment 2 of the meeting package, including appropriate labeling changes would be appropriate for submission as an amendment/ resubmission. They believe that their responses have the potential to address the deficiencies cited in the not approvable letter.

Discussion Points

General

Cellegy presented their responses to the deficiencies listed in the not approvable letter dated December 23, 2004, and they agreed to submit the slides used in their presentation to the NDA. The majority of the discussion focused on the statistical methods and data analyses used for the clinical trials that were conducted in support of approval of nitroglycerin ointment for the relief of pain associated with chronic anal fissure, and risk-benefit issues related to drop-outs and the use of additional mild analgesics in the clinical trials due to headache.

Methods and Data Analyses

The summary of the three clinical studies is as follows:

- Study 1
The primary endpoint of this study was improved healing of chronic anal fissure with the use of topical nitroglycerin (NTG) ointment. This study failed to demonstrate healing, but there appeared to be an effect on a secondary endpoint related to relief of pain.
- Study 2
This study was designed to demonstrate pain relief related to chronic anal fissure. The results of the study were not statistically significant at 56-days (unless one includes a quadratic term), but there was a suggestion of an effect on pain at 21-days.
- Study 3
This study was designed under the guidance of a Special Protocol Assessment (SPA) utilizing the supporting data obtained from the two previous studies. The primary endpoint was relief of pain associated with chronic anal fissure with topical application of NTG ointment at 21-days. The Division determined that the results of this study did not demonstrate a statistically significant effect.

The statistical methods planned for Study 3 were discussed as part of a SPA. The Division had concerns regarding increased drop-outs due to headache, a common side effect for nitroglycerin. Dr. Stockbridge noted that the Division had suggested that Cellegy use a global measurement of "all pain" (including headache) rather than using the "slope-based" analysis, but Cellegy did not adopt that suggestion. The Division had concern for a study that demonstrated significant improvement in anal fissure pain, but where subjects could not stay with the treatment due to headache. The last observation carried forward (LOCF) for patients who stopped treatment due to nitrate induced headache was an attempt to get headache pain factored into the slope that Cellegy planned to use. Dr. Marciniak noted that the efficacy section of the SPA did not specifically describe how NTG-induced headache would be defined.

Cellegy, at that time, stated that they preferred the slope-based approach because of their experience with the two previous studies. It was agreed that the statistical analysis plan would carry the LOCF through day 21 with imputed random error calculations for patients who dropped out of the study due to NTG-induced headache. Cellegy noted that there were only 5 drop-outs due to headache (3 considered NTG-induced) from a sample of 180 subjects, and a pre-specified analysis of the incomplete data was included in the NDA resubmission.

Dr. Temple asked why the analysis should not include the data for all drop-outs up to the point that they dropped out with the last observation carried forward. Cellegy stated that the p-value is <0.03 in an analysis of all data for all subjects (data truncated for drop-outs with no imputation). Dr. Temple stated that the preferred analysis would use all of the data collected for all subjects including drop-outs, and patients who dropped out with headache would be treated the same regardless of attribution. We would need to look at how this analysis was done. Cellegy agreed and stated that they would conduct a reanalysis using all available data and statistically establish curves without imputing data in the reanalysis. (This analysis appears to be similar to one included in the NDA, $p = 0.0306$, also confirmed by the Agency).

Cellegy presented retrospective information on a subset of patients that scored their pain at greater than 50-mm [0 to 100-mm visual analogue scale (VAS)] for 2 days preceding treatment. They reported a p-value of <0.036 for the rate of change through day 21, and a 13.3 and 9.5-mm difference on the VAS at day 15 and 21, respectively. Dr. Temple noted that if the difference was 3 mm for all subjects, the difference for subjects <50-mm at baseline had to be negative. The Agency stated that arbitrarily selecting patients with a >50-mm score needed to be discussed further. Cellegy agreed to provide their rationale and the data to the Agency for comment.

Use of Mild Analgesics

The data in the NDA resubmission noted that patients in the treatment group used more mild analgesics than did the patients in the placebo group, and we do not know if the additional analgesics had an effect on anal pain.

(b) (4) colo-rectal surgical consultant, did not believe that the use of mild analgesics relieved the kind of pain associated with anal fissure. Dr. Marciniak stated that there were no data supporting this assertion, but that a double-blind study comparing the effects of acetaminophen to placebo on anal fissure pain could be done to verify it. Cellegy suggested conducting an analysis on their data to see if analgesics had an effect on anal pain. The possibilities of modeling as a continuous function versus "binning" in groups of 10 (because of the low number of individual scores) were discussed.

Cellegy agreed to look at these data retrospectively and submit their analysis to the Agency for review.

Current Use and Clinically Meaningful Benefits

Cellegy believes that there are clinically meaningful benefits for treating anal pain related to chronic anal fissure with nitroglycerin ointment. They noted that the American Gastroenterological Association and the American Society of Colon and Rectal Surgeons' Standards Task Force recommend the use of NTG ointment before surgical intervention.

Cellegy reported that there were (b) (4) compounded NTG ointment prescriptions written in 2003. An analysis of the extemporaneously compounded NTG prescriptions written by colo-rectal and gastroenterology physicians found that 46% of the prescriptions were out of specifications for content uniformity or potency. Cellegesic is a GMP product with standardized, quantitative dosing.

Conclusions/Recommendations

1. The Agency recommended that Cellegy consider the following:
 - Conduct a reanalysis of the available data for all subjects with no imputation, censoring at the last observation
 - Conduct an analysis of effects of open-label use of mild analgesics on anal pain
 - Conduct an analysis of treatment effect by baseline pain, using the full range of pain, not just a single value (> 50-mm)
2. The Agency concluded that Cellegy could classify and submit the information described above as a resubmission.

Signature Recorder: *{See appended electronic signature page}*
Daryl Allis, R.N., M.S., F.N.P.

Concurrence, Chair: *{See appended electronic signature page}*
Robert Temple, M.D.

Draft:	03/30/05	Final:	04/21/05
RD:			
David	03/31/05		
Hung	04/01/05		
Marciniak	04/4/05		
Karkowsky	04/4/05		
Stockbridge	04/5/05		
Temple	04/21/05		

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

/s/

Daryl L. Allis

4/21/05 04:10:12 PM

A copy of the minutes will be faxed to
the sponsor following Dr. Temple's signature.

Robert Temple

4/25/05 07:08:35 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-359	Efficacy Supplement Type N/A	Supplement Number N/A
Drug: Cellegesic™ (nitroglycerin) 0.4% Ointment		Applicant: Cellegey Pharmaceuticals, Inc.
RPM: Mr. Daryl Allis	HFD-110	Phone # 301-594-5332
Application Type: ☐ 505(b)(1) ☒ 505(b)(2) (This can be determined by consulting page I of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct. ☒ Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 20-145 Nitro-Dur®	
❖ Application Classifications:		
☐ Review priority	☐ Standard ☒ Priority	
☐ Chem class (NDAs only)	3; New Formulation	
☐ Other (e.g., orphan, OTC)	N/A	
❖ User Fee Goal Dates		
January 1, 2005		
❖ Special programs (indicate all that apply)		
☒ None Subpart H ☐ 21 CFR 314.510 (accelerated approval) ☐ 21 CFR 314.520 (restricted distribution) ☐ Fast Track ☐ Rolling Review ☐ CMA Pilot 1 ☐ CMA Pilot 2		
❖ User Fee Information		
☐ User Fee	☒ Paid UF ID number 4141 Resubmission; Fee paid June 2001	
☐ User Fee waiver	☐ Small business ☐ Public health ☐ Barrier-to-Innovation ☐ Other (specify)	
☐ User Fee exception	☐ Orphan designation ☐ No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ☐ Other (specify)	
❖ Application Integrity Policy (AIP)		
☐ Applicant is on the AIP	☐ Yes ☒ No	

Version: 6/16/2004

This application is on the AIP	☐ Yes ☒ No
Exception for review (Center Director's memo)	N/A
OC clearance for approval	N/A
Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	☒ Verified
Patent	
Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified
Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☒ Verified
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	N/A
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i> [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)). <i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i> (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? <i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i> <i>If "No," continue with question (3).</i> (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	☐ N/A (no paragraph IV certification) ☒ Verified ☒ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No

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

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

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

() Yes (X) No

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

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

() Yes (X) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
- Exclusivity summary - Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	N/A
Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.	N/A
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	December 23, 2004

General Information	
❖ Actions	
• Proposed action	☐ AP ☐ TA ☐ AE ☒ NA
• Previous actions (specify type and date for each action taken)	Original NDA withdrawn by the sponsor on 4/25/02
• Status of advertising (approvals only) N/A	☐ Materials requested in AP letter ☐ Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	☐ Yes ☒ Not applicable
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ 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)	N/A
• Most recent applicant-proposed labeling	N/A
• Original applicant-proposed labeling	Yes
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS: 9/24/04; 1/8/02; 7/3/01 DDMAC: N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	Yes
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Yes
❖ Memoranda and Telecons	Yes
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	Not specifically stated
• Pre-NDA meeting (indicate date)	Not specifically stated
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	12/21/04; 4/1/03; 3/20/03; 1/31/03; 6/11/02; 4/24/02; 4/22/02; 4/5/02; 8/15/01; 6/27/01; 1/12/01; 12/7/99; 2/24/98; 1/14/98; 9/25/96
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	December 23, 2004 December 22, 2004 December 20, 2004
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	Dr. Marciniak (Med) 12/17/04 Dr. Fredd 2/27/02 (Med/Stat)
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Page 36; Medical Review 12/17/04
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	Yes; In DFS
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	Dr. Hung 12/17/04 Dr. Hung 2/27/02 (Med/Stat)
❖ Biopharmaceutical review(s) (indicate date for each review)	Dr. Nguyen-Beasley 10/25/04 Dr. Nguyen 3/12/02
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	Ms. Mease/Dr. Ball 12/21/04 Dr. El-Hage 3/19/02
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	Dr. Timmer 12/7 & 12/13/04 Dr. Timmer 4/19/02
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	Acceptable; April 19, 2002
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	Acceptable; April 19, 2002
❖ Facilities inspection (provide EER report)	Date completed: 12/9/04 (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested () Not yet requested N/A
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	Dr. Proakis 8/9/04 Dr. Proakis 4/10/02
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

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/s/

Daryl L. Allis
12/23/04 02:56:26 PM

Minutes of a Teleconference

Meeting Date: December 21, 2004
Application: NDA 21-359 Cellegesic (nitroglycerin) 0.4% Ointment
Sponsor: Cellegy Pharmaceuticals, Inc.

Type of Meeting: C
Classification: Guidance

Meeting Request: December 21, 2004 (Telephone request from Cellegy)
Sponsor Notified: December 21, 2004 (Telephone conversation)
Confirmation Faxed: N/A
Briefing Package Date: N/A

Meeting Chair: Norman Stockbridge, M.D., Ph.D.
Meeting Recorder: Daryl Allis

Attendees:

Division of Cardio-Renal Drug Products

Norman Stockbridge, M.D., Ph.D. Acting Director, Division of Cardio-Renal Drug Products, HFD-110
James Hung, Ph.D. Team Leader, Statistics, HFD-710
Edward Fromm, R.Ph. Chief, Project Management Staff, HFD-110
Daryl Allis, R.N., M.S., F.N.P. Regulatory Health Project Manager, HFD-110

Cellegy Pharmaceuticals, Inc.

Richard Williams Chairman, Board of Directors
K. Michael Forrest CEO and President
David Karlin, M.D. Vice President, Clinical Research
John Chandler Vice President, Corporate Development
JC Lee, Ph.D. Vice President, Development

(b) (4)

Background

Cellegy Pharmaceuticals, Inc (Cellegy) requested this teleconference to discuss their letter of December 14, 2004 responding to the Division's discipline review letter (clinical) for NDA 21-359 [Cellegesic (nitroglycerin) 0.4% Ointment] dated December 10, 2004.

Discussion Points

Cellegy asked whether their response letter of December 14, 2004 answered the Division's questions in our discipline review letter dated December 10, 2004. Dr. Stockbridge explained that we could discuss the open issues, but not the Division's final regulatory action.

There was a general discussion regarding various analyses that might be considered supportive. Dr. Stockbridge stated that if there is an effect from the treatment, it is very small, and the p-value depends on to how the data were analyzed for a few subjects that withdrew for headache, some of which were thought to be not related to the effects of nitroglycerin.

The sponsor agreed that the effect was narrow and the significance was related to a few subjects. However, the primary endpoint agreed upon by the Division under the provisions of a Special Protocol Assessment is the determination of the rate of change (treatment versus placebo) of the 24-hour average pain intensity associated with a chronic anal fissure over a 21-day treatment period. They, therefore, believe that it is important to look at the rate of change for the data for all patients (approximately 700 subjects/ 300 on treatment) for the 21-day period in all three clinical trials that were submitted to this NDA rather than looking at a single 21-day time point. In so doing, they believe the data are persuasive that subjects receiving nitroglycerin treatment got pain relief faster than patients on placebo.

Dr. Stockbridge asked if they applied the same analytic algorithm for the primary analysis for all three trials. Cellegy indicated that they used the same analytical methods for all 3 trials except that they did not know whether headache was likely related to nitroglycerin treatment in the first 2 trials.

Conclusions/Recommendations

- The Division agreed to consider the combined analysis for the rate of change of the 24-hour average pain intensity from baseline through day-21 for the 3 clinical trials.
- Cellegy agreed to provide (within 24-hours) their rationale and perspective for what "more rapid improvement" means and direct the Division to where we could find these analyses in the NDA.

Signature Recorder:

{See appended electronic signature page}
Daryl Allis, R.N., M.S., F.N.P.

Concurrence, Chair:

{See appended electronic signature page}
Norman Stockbridge, M.D., Ph.D.

Draft: 12/22/04
RD:
Fromm 12/22/04
Hung 12/22/04
Stockbridge 12/22/04

Final: 12/22/04

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/s/

Daryl L. Allis

12/22/04 03:15:38 PM

A copy of the minutes will be faxed to
the sponsor after Dr. Stockbridge's final signature.

Norman Stockbridge

12/22/04 03:22:00 PM



NDA 21-359

DISCIPLINE REVIEW LETTER

Cellegy Pharmaceuticals, Inc.
Attention: Daniel L. Azarnoff, M.D, F.A.C.P.
349 Oyster Point Boulevard, Suite 200
South San Francisco, CA 94080-1913

Dear Dr. Azarnoff:

Please refer to your June 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cellegesic™ (nitroglycerin) 0.4% Ointment.

We also refer to your submissions dated September 3, 21, 28, & 30; October 5, 6, 22, & 26; and November 3 & 19, 2004.

Our review of the Clinical section of your submissions is complete, and we have identified the following issues, upon which you are invited to comment:

1. The protocol says that imputation would be applied to subjects who withdrew for reasons of headache, but in the analyses of study 03-02-01, imputation was restricted to subjects whose headaches were attributed to study drug. How is this justified?
2. Four subjects randomized to nitroglycerin ointment (NTG) in study 03-02-01 have no data post-randomization. Seven more NTG subjects discontinued prior to 21 days. No placebo subjects did. What are the implications on the interpretability of the findings of study 03-02-01 of having the observed imbalance between groups in the number of subjects withdrawn in the first 21 days?
3. What is the plausible clinical significance of a 3-mm mean difference in the anal pain visual analog scale, when this magnitude of effect is 13% of the placebo effect, and how does this difference balance against a high rate of withdrawal for headache and other adverse effects?
4. In study 03-02-01 one NTG patient withdrew because of dizziness, bradycardia, and extrasystoles and another withdrew because of tachycardia, both adverse events suggestive of systemic cardiovascular effects of NTG absorption. Your pharmacokinetic study documented about 50% bioavailability of NTG with wide variability ($\pm 30\%$). How well does your clinical safety database characterize the variability in systemic cardiovascular effects of NTG ointment, e.g., time course of vital signs post-administration in patients and during cardiovascular adverse events? How much assurance does your clinical safety database provide of cardiovascular safety, particularly for patients with underlying cardiovascular disease? How do these potentially serious adverse effects balance against a minimal symptomatic benefit?
5. Only 19 patients aged 65 or older completed treatment with 0.4% NTG BID in your studies. Your proposed label suggests that "Clinical data from the published literature indicate that the elderly demonstrate increased sensitivity to nitrates, which may reflect the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy." How does the exposure in your studies support safe administration in the elderly?

NDA 21-359
Discipline Review Letter: Clinical
Page 2

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we 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:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5332.

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
12/10/04 12:45:37 PM

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
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5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

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Transmitted to FAX Number: 650-616-2222

Attention: Dr. Azarnoff

Company Name: Cellegy Pharmaceuticals, Inc.

Phone: 650-616-2200

Subject: CMC: Request for information

Date: 11/9/04

Pages including this sheet: 2

From: Daryl Allis
Phone: 301-594-5332
Fax: 301-594-5494
E-mail: allisd@cder.fda.gov

Dr. Azarnoff,

Please see the attached page requesting additional CMC information.

Thank you,

Daryl Allis, Project Manager

INFORMATION REQUESTS FOR NDA 21-359 RESUBMISSION:

1. Please state the retest date for the drug substance? That is, how long can the (b) (4) sit in its shipping container in the warehouse before it needs to be retested for compliance to the raw material specifications?
2. Regarding test (b) (4)-0038-LC*: *Quantitation and identification of nitrogen related substances in the Ointment*, please develop a numerical specification (or limit) for each impurity as well as a total impurity limit. This request applies to impurity testing for the drug substance, after manufacture of the ointment, and during the stability program.
3. Please correct the 'Specification' tables for viscosity. Presently the tables list, under viscosity, the specification of "Report Value." The tables should be corrected to reflect the viscosity specification of (b) (4) cps.
4. Please submit color mock-ups of the carton and label.

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



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Rockville, MD 20857

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Transmitted to FAX Number: 650-616-2222

Attention: **Dr. Daniel Azarnoff**

Company Name: Cellegey Pharmaceuticals, Inc

Phone: 650-616-2214

Subject: NDA 21-359: Statistical information

Date: 10/29/04

Pages including this sheet: 2

From: **Daryl Allis**
Phone: **301-594-5332**
Fax: **301-594-5494**
E-mail: **allisd@cdcr.fda.gov**

Dr. Azarnoff,

The statistician requests that you provide the following information:

Three cellegesic dropouts had missing values imputed due to headaches according to the sponsor's supplied SAS program.

Patient '037-380' had average pain data at least up to Day 21 (i.e., AVGPAIN were available). Why were the data of this patient for Day 10-21 imputed (i.e., AVGPAIN2 differs from AVGPAIN)? Please see the attachment on the following page.

Regards,
Daryl

obs	SUBJID	trt	days	AVGPAIN	AVGPAINZ
1	008-052	0.4%	0	65.5	65.5000
2	008-052	0.4%	1	25.0	25.0000
3	008-052	0.4%	2	9.0	9.0000
4	008-052	0.4%	3	21.0	21.0000
5	008-052	0.4%	4	33.0	33.0000
6	008-052	0.4%	5	13.0	13.0000
7	008-052	0.4%	6	13.0	13.0000
8	008-052	0.4%	7	19.0	19.0000
9	008-052	0.4%	8	23.0	23.0000
10	008-052	0.4%	9	.	34.5811
11	008-052	0.4%	10	.	24.5806
12	008-052	0.4%	11	.	20.6441
13	008-052	0.4%	12	.	7.8360
14	008-052	0.4%	13	.	12.7137
15	008-052	0.4%	14	.	34.1561
16	008-052	0.4%	15	.	28.8896
17	008-052	0.4%	16	.	26.7643
18	008-052	0.4%	17	.	12.1739
19	008-052	0.4%	18	.	18.8096
20	008-052	0.4%	19	.	19.6487
21	008-052	0.4%	20	.	29.1350
22	008-052	0.4%	21	.	10.8444
23	037-159	0.4%	0	42.0	42.0000
24	037-159	0.4%	1	37.0	37.0000
25	037-159	0.4%	2	32.0	32.0000
26	037-159	0.4%	3	56.0	56.0000
27	037-159	0.4%	4	.	44.7652
28	037-159	0.4%	5	.	45.3780
29	037-159	0.4%	6	.	62.6176
30	037-159	0.4%	7	.	61.9000
31	037-159	0.4%	8	.	54.5323
32	037-159	0.4%	9	.	48.0053
33	037-159	0.4%	10	.	52.0985
34	037-159	0.4%	11	.	69.0759
35	037-159	0.4%	12	.	54.9723
36	037-159	0.4%	13	.	43.4422
37	037-159	0.4%	14	.	66.5776
38	037-159	0.4%	15	.	58.8147
39	037-159	0.4%	16	.	45.0677
40	037-159	0.4%	17	.	42.3057
41	037-159	0.4%	18	.	42.9723
42	037-159	0.4%	19	.	63.4768
43	037-159	0.4%	20	.	45.7049
44	037-159	0.4%	21	.	70.2441
45	037-380	0.4%	0	43.5	43.5000
46	037-380	0.4%	1	37.0	37.0000
47	037-380	0.4%	2	24.0	24.0000
48	037-380	0.4%	3	30.0	30.0000
49	037-380	0.4%	4	38.0	38.0000
50	037-380	0.4%	5	0.0	0.0000
51	037-380	0.4%	6	47.0	47.0000
52	037-380	0.4%	7	27	27.0000
53	037-380	0.4%	8	0	0.0000
54	037-380	0.4%	9	0	0.0000
55	037-380	0.4%	10	22	11.0483
56	037-380	0.4%	11	34	0.0000
57	037-380	0.4%	12	38	0.0000
58	037-380	0.4%	13	53	2.8823
59	037-380	0.4%	14	62	11.8470
60	037-380	0.4%	15	70	12.8275
61	037-380	0.4%	16	61	0.0000
62	037-380	0.4%	17	67	1.8218
63	037-380	0.4%	18	56	6.9704
64	037-380	0.4%	19	43	18.4835
65	037-380	0.4%	20	48	17.3430
66	037-380	0.4%	21	22	14.5686



NDA 21-359

INFORMATION REQUEST LETTER

Cellegy Pharmaceuticals, Inc.
Attention: Daniel L. Azamoff, M.D, F.A.C.P.
349 Oyster Point Boulevard, Suite 200
South San Francisco, CA 94080

Dear Dr. Azamoff:

Please refer to your June 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cellegesic™ (nitroglycerin) 0.4% Ointment.

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.

Your letter dated September 21, 2004, states that Randomization Table A was used for the US and Randomization Table B was used for Europe. The second letter in Attachment 1 of your September 21, 2004, submission states that Table A was to be used the first time a block was assigned to a site and then Table B was used to be used the second time. This latter approach appears to have been used.

1. Operationally how was randomization done in the US? In Europe? Please describe your planned and actual randomization and drug distribution procedures in both the US and Europe. Please detail actions taken by all participants: (b) (4) Cellegy, Drug Distribution Center, Statistical Center, sites, and any other entity involved in randomization or drug distribution and dispensing.
2. Randomization Tables A and B do not include space to record that an entry has been assigned. How was entry assignment recorded and tracked?
3. How was medication sent to the site tracked? Please provide a tabulation of all drug supplies sent to the sites and their disposition.
4. Why are randomization numbers assigned to a site in great excess of what is stated to be randomized? For example, site 022 enrolled one patient but has one block assigned in Table A and 2 blocks assigned in Table B.
5. How were block numbers assigned to sites? Block 1 appears to be assigned to the site with earliest enrollment, but block 2 is assigned to a site that enrolled patients late. What was the procedure specified to be used if a site enrolled more than 8 patients?
6. Your protocol states that randomization numbers for European subjects were to start with 200. Why was that not done?
7. Why were blocks 45 through 70 skipped in Table B? Explain how this is or is not a violation of your randomization protocol.
8. Why was the first entry for block 13 (subject ID 49) not used but entries 2 and 3 were?
9. Why was the second entry for block 82 (subject ID 326) the only entry in this block not used?

NDA 21-359
Information Request: Clinical
October 12, 2004

2

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Edward Fromm
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/

Edward Fromm
10/12/04 10:18:18 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-359

Cellegy Pharmaceuticals, Inc.
Attention: Daniel L. Azarnoff, M.D, F.A.C.P.
349 Oyster Point Boulevard, Suite 200
South San Francisco, CA 94080

Dear Dr. Azarnoff:

Please refer to your pending new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cellegesic™ (nitroglycerin) 0.4% Ointment.

We also refer to our acknowledgment letter dated August 3, 2004, that stated the drug review priority classification for this application would be standard (S).

Our policy regarding determination of priority or standard review status is based on the proposed indication and alternative treatment marketed for the proposed indication. Upon further consideration of your application and letter, dated September 28, 2004, requesting clarification or reclassification/appeal for a priority review, we have concluded that this application should receive a priority review. The new user fee goal date is January 1, 2005.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Edward Fromm
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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Edward Fromm
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From the CDER Electronic Document Room Staff

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5901-B Ammendale Rd.
Beltsville, MD 20705

To Contact: **David Karlin**

Fax: **650-616-2222**

Phone: **650-616-2200**

Re: Firm: **Cellegy**

Application **N21359**

Letter Date: **9/21/04**

RESUBMISSION REQUIRED

☒	1. Document(s) submitted in non archival format (MS Word, etc.) – documents other than draft labeling text, should only be submitted in PDF format described in the guidance(s).
☐	2. Labeling was submitted in MS Word format as described in the guidance, but without a corresponding PDF rendition - labeling should be submitted in PDF format. Draft labeling text may also be submitted in MS Word format, but all labeling submitted in word processing format should be accompanied in the submission by a PDF rendition.
☒	3. Data set(s) submitted in non archival format(s) – SAS transport V5 as per SAS TS-140 (XPORT) is the format specified by the guidance.
☐	4. Other -

RESUBMISSION NOT REQUIRED

Your electronic records may have been delayed for the following reasons, but No further action is necessary at this time. Please address these issues in future submissions.

☐	1. Electronic Submission submitted to wrong address – If electronic components are included, submit entire submission (paper and electronic components) only to the CDR (see address above).
☒	2. Duplicate copies of electronic media submitted - Submit only 1 set of electronic media, submitting a duplicate copy of electronic media may delay review and is unnecessary.
☒	3. Electronic Table of Contents, e356h form and/or eCover Letter) not submitted - Including electronic PDF renditions of these paper documents, will help speed up the document room process.
☐	4. Other –

For assistance or questions contact:

Office of Information Management – Ken Edmunds

Email (preferred) ESUB@CDER.FDA.GOV Phone: 301-827-7706

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-359

Cellegy Pharmaceuticals, Inc.
Attention: Daniel L. Azarnoff, M.D., F.A.C.P.
349 Oyster Point Boulevard, Suite 200
South San Francisco, CA 94080-1913

Dear Dr. Azarnoff:

Please refer to your new drug application (NDA), dated June 30, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cellegesic™ (nitroglycerin) Nitroglycerin 0.4% Ointment.

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 August 30, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

The patent certification for the reference listed drug, Nitro-Dur (NDA 20-145), was not submitted.

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.

If you have any questions, please call Mr. Daryl Allis, Regulatory Project Manager, at (301) 594-5332.

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
9/9/04 04:44:47 PM



NDA 21-359

INFORMATION REQUEST LETTER

Cellegy Pharmaceuticals, Inc.
Attention: Daniel L. Azarnoff, M.D., F.A.C.P.
349 Oyster Point Boulevard, Suite 200
South San Francisco, CA 94080-1913

Dear Dr. Azarnoff:

Please refer to your June 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cellegesic™ (nitroglycerin) Nitroglycerin 0.4% Ointment.

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.

1. Section 2.5 Randomization, p. 27, of the Study Report for CP125 describes a subject number based on a 3-digit investigator number combined with a 3-digit sequence number assigned sequentially, starting with 001 for US subjects and 200 for European subjects. The subjid variable in the SAS data sets is similar to this definition but the sequence number portion has many gaps in sequential assignments.
 - a. Please explain how the protocol definition of a subject number and subjid relate.
 - b. Please provide a data set with the protocol-defined subject number, subjid (if not the protocol-defined subject number), and site for all protocol-defined subject numbers used. Please include a variable describing the reason that any protocol-defined subject number was not used in the analyses.
 - c. Please explain any gaps in the protocol-defined subject numbers and in subjid.
2. Please provide a copy of the computer-generated randomization schedule prepared by FRI Solutions, Inc. for Study CP125. Please account for all randomizations numbers used and provide the protocol-defined subject numbers and subjid for all randomization numbers used.
3. The protocol estimates a study size of 150 but 193 patients were analyzed. Please explain.
4. Please provide the following numbers:
 - a. Subjects screened
 - b. Subjects enrolled (if different than subjects randomized)
 - c. Subjects randomized
5. Please provide a SAS data set with subjid and all data points for your primary efficacy analysis for Study CP125. Include LOCF values and a variable identifying which values are LOCF values. Also provide a SAS program to duplicate your primary efficacy results from this data set.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5309

Sincerely,

{See appended electronic signature page}

Edward Fromm
Acting 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/

Edward Fromm
9/1/04 02:12:04 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-359

Cellegy Pharmaceuticals, Inc.
Attention: Daniel L. Azarnoff, M.D., F.A.C.P.
349 Oyster Point Boulevard
Suite 200
South San Francisco, CA 94080-1913

Dear Dr. Azarnoff:

Please refer to your submission dated June 30, 2004, requesting a deferral of pediatric studies for Cellegesic™ (nitroglycerin) Nitroglycerin 0.4% Ointment.

We have reviewed the submission and agree that a deferral of pediatric studies in patients ages <1 to 16 years is justified for Cellegesic™ (nitroglycerin) Nitroglycerin 0.4% Ointment for relief of pain associated with chronic anal fissure because the drug would be ready for approval in adults before studies in children would be completed. We, however, request that you submit a general plan and timeline for your pediatric development program to the Division by December 27, 2004.

Accordingly, pediatric studies are deferred for your application under 21 CFR 314.55 until May 1, 2007.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Project Manager
301-594-5309

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
8/26/04 12:52:44 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-359

INFORMATION REQUEST LETTER

Cellegy Pharmaceuticals, Inc.
Attention: Daniel L. Azarnoff, M.D., F.A.C.P.
349 Oyster Point Boulevard, Suite 200
South San Francisco, CA 94080-1913

Dear Dr. Azarnoff:

Please refer to your June 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cellegesic™ (nitroglycerin) Nitroglycerin 0.4% Ointment.

We are reviewing the Biopharmaceutical section of your submission and we request that you submit the assay validation information for the pharmacokinetic study.

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5309

Sincerely,

{See appended electronic signature page}

Edward Fromm
Acting 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/

Edward Fromm
8/18/04 09:37:12 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-359

Cellegy Pharmaceuticals, Inc.
Attention: Daniel L. Azarnoff, M.D., FACP
349 Oyster Point Blvd, Suite 200
South San Francisco, CA 94080-1913

Dear Dr. Azarnoff:

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

Name of Drug Product: Cellegesic™ (nitroglycerin) 0.4% Ointment

Review Priority Classification: Standard (S)

Date of Application: June 30, 2004

Date of Receipt: July 1, 2004

Our Reference Number: NDA 21-359

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 August 30, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 1, 2005.

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 acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

NDA 21-359

Page 2

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 of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5309

Sincerely,

{See appended electronic signature page}

Edward Fromm
Acting 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/

Edward Fromm
8/3/04 02:12:41 PM

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached lists	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
David A. Karlin, MD	Vice President, Clinical Research
FIRM/ORGANIZATION	
Cellegy Pharmaceuticals, Inc.	
SIGNATURE	DATE
<i>David A. Karlin, MD</i>	6/11/2004

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

This is to certify that Cellegy Pharmaceuticals, Inc. has on file the financial disclosure FDA Form 3454 for the following study personnel who were listed on the FDA 1572 for study (b) (6) None of those listed have a financial conflict of interest:



(b) (6)

(b) (6)





After two attempts, Cellegy was unable to contact the following people:



David A. Karlin, MD

David A. Karlin, MD
Vice President, Clinical Research

This is to certify that Cellegy Pharmaceuticals, Inc. has on file the financial disclosure FDA Form 3454 for the following study personnel who were listed on the FDA 1572 for study (b) (6). None of those listed have a financial conflict of interest:



(b) (6)

(b) (6)



(b) (6)



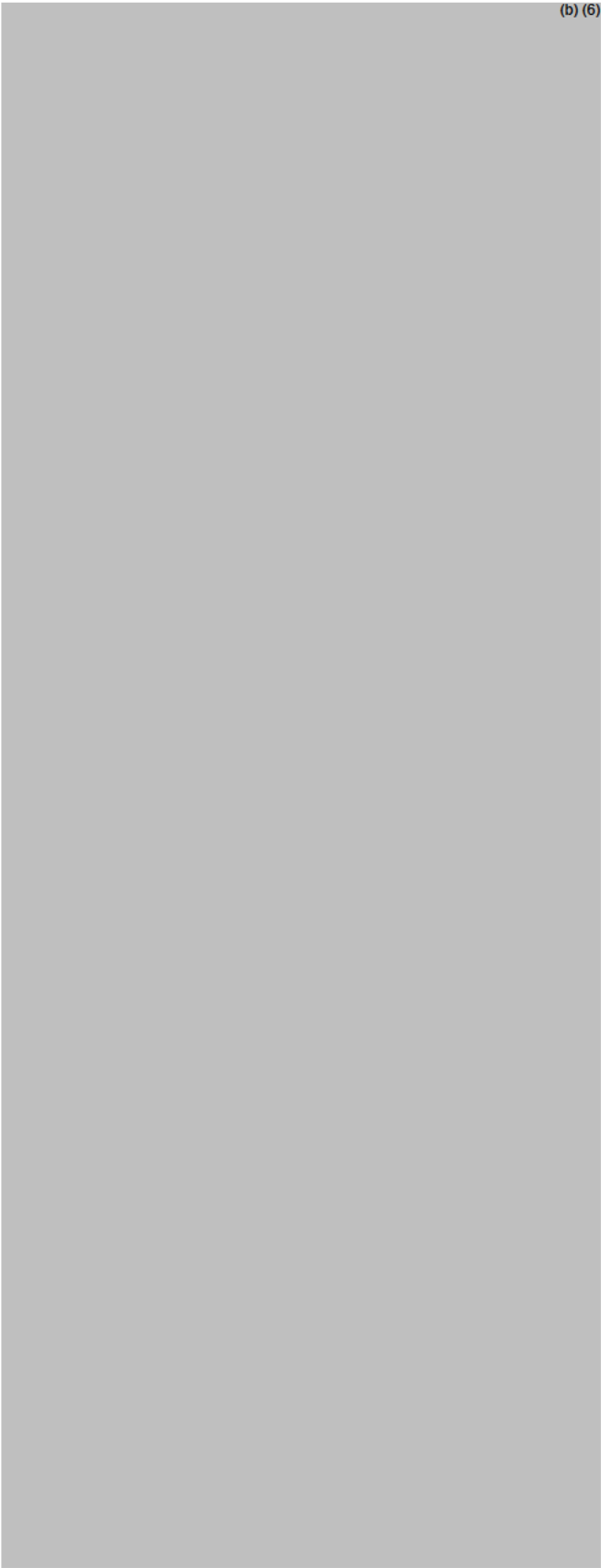
After two attempts, Cellegy was unable to contact the following people:



David A. Karlin, MD

David A. Karlin, MD
Vice President, Clinical Research

(b) (6)



(b) (6)



(b) (6)



(b) (6)



David A. Karlin, MD

David A. Karlin, MD
Vice President, Clinical Research

4/1/02

To: NDA 21359

From: Stephen Fredd, M.D., HFD-110

Subject: Financial Disclosure, Study (b) (6)

On 11/16/01 Cellegy Pharmaceuticals Inc. submitted the financial disclosure information for study (b) (6) Dr. Azarnoff, Sr. Vice President, Clinical Regulatory Affairs certified by checking box (1) on FDA form 3454 that they have not entered into any financial arrangement with the listed investigators where the value of compensation could be affected by the outcome of the study. The sponsor also certified that each listed clinical investigator disclosed that he or she had no proprietary interest in the product and no significant equity in the sponsor.

The (b) (6) investigators on the attached list whose data are on file at the company were participants in study (b) (6) The company notes that they were unable to contact (b) (6) investigators. It appears that the sponsor has submitted the requisite financial disclosure information.

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/s/

Stephan Fredd
4/2/02 08:36:49 AM
MEDICAL OFFICER

3/26/02

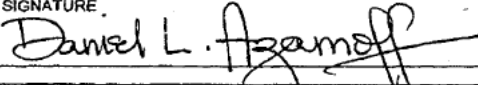
To: NDA 21359
From: Stephen Fredd, M.D.
Subject: Financial Disclosure Information

On 6/22/2001, the sponsor provided a certification re the financial interests and arrangements of clinical investigators. The certification chosen is number 1 on the form, whereby the sponsor stated they have not entered into any financial arrangement with the listed investigators where the value of compensation could be affected by the outcome of the study. The sponsor also certified that each listed clinical investigator disclosed that he or she had no proprietary interest in the product and no significant equity in the sponsor. The investigators listed were participants in studies (b) (4), (b) (6), (b) (3) (B). The sponsor was unable to contact (b) (4), (b) (6), (b) (3) (B) investigators. The pivotal study (b) (4), (b) (6), (b) (3) (B) is not included. This financial disclosure information is therefore incomplete. It should be updated to include study investigators who participated in study (b) (4), (b) (6), (b) (3) (B).

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/s/

Stephan Fredd
3/26/02 09:53:08 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration	Form Approved: OMB No. 0910-0396 Expiration Date: 3/31/02						
CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS							
TO BE COMPLETED BY APPLICANT							
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).							
Please mark the applicable checkbox.							
☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).							
Clinical Investigators	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">See attached list</td> <td style="width: 50%;"></td> </tr> <tr> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> </tr> </table>	See attached list					
See attached list							
☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).							
☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.							
NAME Daniel L. Azarnoff, MD	TITLE Sr. Vice President, Clinical/Regulatory Affairs						
FIRM/ORGANIZATION Cellegy Pharmaceuticals, Inc.							
SIGNATURE 	DATE May 7, 2001						
Paperwork Reduction Act Statement							
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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:							
Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 14C-03 Rockville, MD 20857							

This is to certify that Cellegy Pharmaceuticals, Inc. has on file the financial disclosure FDA Form 3454 for the following study personnel who were listed on the FDA 1572 for study (b) (4), (b) (6), (b) (3) (B) None of those listed have a financial conflict of interest:



(b) (6)

NDA 21-359 Anogesic®
Nitroglycerin Ointment 0.2% and 0.4%,
USP
Cellegy Pharmaceuticals, Inc.

19; v01; p004

(b) (6)



NDA 21-359 Anogesic®
Nitroglycerin Ointment 0.2% and 0.4%, USP
Cellegy Pharmaceuticals, Inc.

19; v01; p005

After two attempts, Cellegy was unable to contact the following people:



(b) (6)

Daniel L. Azarnoff, M.D.
Sr. Vice President, Clinical/Regulatory Affairs

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

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Transmitted to FAX Number: (650) 616-2222

Attention: Dr. William Schary

Company Name: Cellegy Pharmaceuticals

Phone: (650) 616-2215

Subject: **Dr. Hung's Comments for IND 45,326**
Ser# 53
Sponsors submission dated 4/9/03
Nitroglycerin Ointment for Anal Fissures

Date: May 16, 2003

Pages including this sheet: 1

From: Edward Fromm

Phone: 301-594-5332

Fax: 301-594-5494

In this submission, the sponsor requested clarification of four points from the Agency's 3/20/2003 meeting minutes. One statistical point pertains to the analysis plan for the five secondary endpoints. My comments below on this point need to be conveyed to the sponsor.

The meeting minutes conveyed a need to specify an analysis plan for the five secondary endpoints if the primary endpoint wins. The overall type I error rate would be at issue if any of the secondary endpoints that result in positive results are to be included in labeling. Thus, the method for testing the secondary endpoints needs to control the overall type I error rate (usually, at a two-sided 0.05 level). One strategy is to specify a sequence for testing the secondary endpoints if the primary endpoint wins. Provided that the primary endpoint reaches statistical significance, each secondary endpoint can be tested at two-sided $\alpha = 0.05$ until a nonsignificant endpoint is found. Another strategy is to let the p-values of the secondary endpoints determine the order of testing. Holm's step-down method can be used in this case. That is, after the primary endpoint wins, the smallest p-value of the secondary endpoints will be compared with 0.01 ($=0.05/5$) to determine its significance. If it is significant, then compare the next smallest p-value with 0.0125 ($=0.05/4$) to determine its significance. The process stops when a nonsignificant p-value is found.

In any event, the protocol needs to specify the statistical method for testing the five secondary endpoints.

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/s/

Edward Fromm
5/16/03 08:41:11 AM
CSO

Minutes of a Telecon between Cellegy Pharmaceuticals and the FDA Cardio-Renal Division

Date: April 1, 2003
Applications: IND 45,326
Cellegesic (nitroglycerin ointment)
Applicant: Cellegy Pharmaceuticals, Inc.
Subject: Clinical Development

FDA Participants:

Douglas C. Throckmorton, M.D., HFD-110, Division Director, Cardio-Renal Drug Products
Edward Fromm, HFD-110, Regulatory Health Project Manager

Cellegy Pharmaceuticals

Mr. K. Michael Forrest, CEO and President
Daniel Azarnoff, M.D., Senior Vice President, Regulatory and Medical Affairs
David Karlin, Vice President, Clinical Research and Development
William Schary, Ph.D., Vice President, Regulatory Affairs

(b) (4)

Background

On June 25, 2001, Cellegy submitted a 505(b)(2) application for Cellegesic Ointment (0.2 and 0.4% nitroglycerin) intended for use intra-anally at the site of an anal fissure and indicated for relief of pain associated with chronic anal fissures. Because of significant deficiencies in the application, the sponsor withdrew their NDA application on April 25, 2002. Follow-up discussions with the Agency have identified the need to conduct an additional study to assess the efficacy of the product.

Cellegy submitted a revised protocol dated September 16, 2002, for a special clinical protocol assessment. The protocol was entitled CP 125 02-02-02, "*A Study to Determine the Effect of CP 125 Ointment on the Pain Associated with a Chronic Anal Fissure*".

After several discussions regarding this protocol by the Division and the sponsor, agreement was reached on a final protocol with one notable exception, the timing of the pain assessment done by the patient. The sponsor has asked that this assessment be done at bedtime but the Division is not comfortable with this arrangement without data describing the temporal relationship of pain relief and application of the ointment. The telecon today is to try to reach agreement on this item so the sponsor can begin enrolling patients for the study.

Telecon

Dr. Throckmorton opened the telecon by noting that he had reviewed the sponsor's submission dated March 26, 2003 and had found the changes made to protocol acceptable but had not found a proposal to study a cohort of patients to determine the temporal relationship between pain relief and application of the ointment. He mentioned that he had discussed the idea of collecting data in a subset of patients for this purpose with Dr. Temple and that Dr. Temple had agreed to this approach for collecting these data. The data collected would be very useful for describing the effects of the drug in labeling but would not be used by the Agency to invalidate the results of the study.

Cellegy asked how the Division envisioned collection of these data. Could they ask the patient "was your pain relief greater after 1-2 hours after applying the ointment or consistent between doses of the drug"?

Dr. Throckmorton said this question was a bit leading and suggested that the collection of the data could be done in a small number of patients at the beginning of the study for several days. Pain measurements after application of the ointment could be done, for example, at 1, 2, 4 and 8 hours and would give a better idea of pain relief throughout the day. He emphasized that the sponsor did not have to prove that the ointment was better than placebo in this cohort of patients, although it could provide additional data on efficacy were it to be found.

Cellegy said they would agree to study a cohort of patients to better define the temporal relationship between pain relief and application of the ointment and asked if they would need to submit the revisions to the Agency before initiating the study. Dr. Throckmorton replied that he did not want to delay the study any further and therefore it was not necessary to submit the revisions for review before starting the study. The sponsor said they appreciated the Division's feedback on the protocol and said they would notify the Division when they had a proposal ready for submission.

The sponsor asked what type of review (priority or standard) the application would receive when submitted as a NDA. Dr. Throckmorton said that a determination of the review status for the application would not be known until the application was submitted. Mr. Fromm noted that the application would receive a standard (10 month clock) review unless the Division determined that a priority (6 month clock) was warranted. He added that had the sponsor elected to receive a not approvable letter instead of withdrawing the application, then the review clock would have been 6 months once the sponsor submitted a complete response to the deficiencies listed in the not approvable letter.

Minutes Preparation:

Edward Fromm

Concurrence Chair:

Douglas C. Throckmorton, M.D.

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/s/

Edward Fromm

4/3/03 01:22:10 PM

CSO

Dr. Throckmorton signed the minutes on April 3, 2003.

Minutes of a Telecon between Cellegy Pharmaceuticals and the FDA Cardio-Renal Division

Date: March 20, 2003
Applications: IND 45,326
Cellegesic (nitroglycerin ointment)
Applicant: Cellegy Pharmaceuticals, Inc.
Subject: Clinical Development

FDA Participants:

Douglas C. Throckmorton, M.D., HFD-110, Division Director, Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., HFD-110, Deputy Division Director
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Salma Lemtouni, M.D., M.P.H., HFD-110, Medical Officer
James Hung, Ph.D., HFD-710, Statistician/Team Leader
John Lawrence, Ph.D., HFD-710, Statistician
Charles Anello, Sc.D., HFD-700, Office of Biostatistics
Edward Fromm, HFD-110, Regulatory Health Project Manager

Cellegy Pharmaceuticals

Mr. K. Michael Forrest, CEO and President
Daniel Azarnoff, M.D., Senior Vice President, Regulatory and Medical Affairs
David Karlin, Vice President, Clinical Research and Development
William Schary, Ph.D., Vice President, Regulatory Affairs

(b) (4)

Background

On June 25, 2001, Cellegy submitted a 505(b)(2) application for Cellegesic Ointment (0.2 and 0.4% nitroglycerin) intended for use as a self-administered treatment to be applied intra-anally at the site of an anal fissure and indicated for relief of pain associated with chronic anal fissures. Because of major deficiencies with the application identified by the Agency, the sponsor withdrew their application on April 26, 2002.

Cellegy submitted a revised protocol dated September 16, 2002, for a special clinical protocol assessment. The protocol was entitled CP 125 02-02-02, "*A Study to Determine the Effect of CP 125 Ointment on the Pain Associated with a Chronic Anal Fissure*". The Division replied, in a letter dated November 1, 2002, with comments and clarifications on the sponsor's proposed study.

Following a meeting with the Agency on January 31, 2003, the sponsor sent revisions to their protocol in submissions dated February 13 and 27, 2003. The telecon today is to discuss these revisions and to determine whether they are sufficient to allow the study to proceed.

Telecon

Statistical Issues

- Page 5, topic 11.1 of sponsor's submission dated February 27, 2003: Carrying the last observation forward for patients who discontinue may result in a biased analysis even if the mean pain score would remain constant from the time of discontinuation for these patients. This is because the estimate of the variance of the residual error

may be consistently lower than the true variance. A suggestion was made to modify the carried forward constant values by simulating observations with mean equal to the last observed value and variance equal to the estimated residual variance from a repeated measurements model.

- Dr. Throckmorton noted that the sponsor had chosen 5 secondary endpoints without specifying which one would be meaningful with regard to the labeling of the study drug if the primary endpoint were met. Therefore, the sponsor needs to specify a method for controlling the overall error rate. One way to control the overall error rate is to pre-specify a sequence for testing the secondary endpoints. If the sequence is pre-specified, then each endpoint can be tested (at two-sided $\alpha = 0.05$) provided the testing stops after a non-significant p-value is found. Cellegy said they will revise their protocol accordingly to include the statistical plan for the 5 secondary endpoints but noted that time to 50% improvement would likely have the highest ranking.

Clinical Issues

- In reference to the study question asking patients about what treatment they thought they were receiving, specified in the protocol for day 56, Dr. Throckmorton suggested moving this question to day 21 because of potential loss to follow-up and the difficulty of keeping patients blinded after they are no longer taking the study drug.
- Page 4, topic 9.1: Dr. Throckmorton said a more precise definition of what “clinically significant” adverse events is needed. Cellegy said it was their intention to let the investigators of the study make this determination; nevertheless they said they would attempt to come up with a more precise definition.
- Dr. Throckmorton noted that the Time and Events Schedule included in the February 27, 2003 submission contain only references to the December 3, 2002 version of the protocol and not the most recent one. He asked that the sponsor send in a more current version of the schedule if different from that included with this last submission.
- Dr. Throckmorton noted that the trial results could be confounded by the intake of concomitant treatments and/or medications such as headache medication and sitz baths, and suggested that the sponsor do everything possible to ensure unambiguous interpretability of the data.
- Temporal relationship between application of the ointment and pain relief-Dr. Throckmorton said the data submitted from colorectal surgeons who have prescribed the drug was insufficient to determine if the drug’s effect on pain relief is gradual or is quick with a tapering effect throughout the rest of the day. He suggested that the sponsor follow-up with patients in previous studies to obtain these data.

Cellegy replied that they did not have ready access to these patients and said that even if they could collect such data it would likely be subjective and difficult to interpret. They asked if they could collect the time to pain-relief data prospectively as part of the main study. Dr. Throckmorton expressed concern that even with a prospective collection of the data, the optimal inter-dosing interval may not be calculated. Nevertheless, he said he would discuss the sponsor’s proposal with Dr. Temple and communicate the results of that discussion to the sponsor as soon as possible.

Minutes Preparation:

Edward Fromm

Concurrence Chair:

Douglas C. Throckmorton, M.D.

dr: ef/3/24/03-4/01/03

Rd: NStockbridge-3/27/03
SLemtouni-3/27/03
JLawrence-3/25/03
JHung-3/25/03

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/s/

Edward Fromm

4/2/03 12:12:55 PM

CSO

Dr. Throckmorton signed the minutes on April 2, 2003

Minutes of a Meeting between Cellegy Pharmaceuticals and the FDA Cardio-Renal Division

Date: January 31, 2003
Applications: IND 45,326
Cellegesic (nitroglycerin ointment)
Applicant: Cellegy Pharmaceuticals, Inc.
Subject: Clinical Development

FDA Participants:

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research
Douglas C. Throckmorton, M.D., HFD-110, Division Director, Cardio-Renal Drug Products
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Salma Koessel, M.D., Ph.D., HFD-110, Medical Officer
Robert O'Neill, Ph.D., HFD-700, Director, Office of Biostatistics
James Hung, Ph.D., HFD-710, Statistician/Team Leader
John Lawrence, Ph.D., HFD-710, Statistician
Charles Anello, Sc.D., HFD-700, Office of Biostatistics
George Chi, Ph.D., HFD-710, Director, Division of Biometrics
Edward Fromm, HFD-110, Regulatory Health Project Manager

Cellegy Pharmaceuticals

Mr. K. Michael Forrest, CEO and President
Daniel Azarnoff, M.D., Senior Vice President, Regulatory and Medical Affairs
David Karlin, Vice President, Clinical Research and Development
William Schary, Ph.D., Vice President, Regulatory Affairs

(b) (4)

Background

On June 25, 2001, Cellegy submitted a 505(b)(2) application for Cellegesic Ointment (0.2 and 0.4% nitroglycerin) intended for use as a self-administered treatment to be applied intraanally at the site of an anal fissure and indicated for relief of pain associated with chronic anal fissures. Because of major deficiencies with the application identified by the Agency, the sponsor withdrew their application on April 26, 2002.

Cellegy submitted a revised protocol dated September 16, 2002, for a special clinical protocol assessment. The protocol was entitled CP 125 02-02-02, "*A Study to Determine the Effect of CP 125 Ointment on the Pain Associated with a Chronic Anal Fissure*". The Division replied, in a letter dated November 1, 2002, with comments and clarifications on the sponsor's proposed study.

Cellegy, in a submission dated December 4, 2002, asked for a meeting to discuss several issues that are still outstanding. The meeting today is to discuss these issues and try to clear up areas of disagreement so as to enable the pivotal trial to begin.

Meeting

Statistical Issues

Dr. Throckmorton opened the meeting by noting that the statistical analysis plan for the study appears to be acceptable, although it does not use a categorical analysis as the Agency prefers. Dr. Hung conveyed that the Agency statisticians still have some concerns about the statistical analysis plan. One question that remains is how dropouts will be analyzed statistically. We understand that the sponsor plans to impute a LOCF (Last Observation Carried Forward) value for patients that drop out due to headaches, but there may be other reasons a patient drops out of the study. If there are a large number of dropouts (for any reason), then unless follow-up is planned after the study is completed, the interpretation of the study results will depend on assumptions that cannot be verified by the data. In addition, imputing a fixed LOCF value for patients who dropout for headache may result in underestimation of the variance. Dr. O'Neill noted that without collection of data on all patients who drop out of the study, it is possible that informative censoring of the data may bias the results. He pointed out, for example, that some patients might, in fact, have a rebound effect when stopping the use of the ointment.

Cellegy replied that they could take the estimated variance from LOCF and resample with a normal distribution. They noted, however, that they believe that patients who dropout of the study due to headache can be ignored from a statistical standpoint. The sponsor said they have done extensive analyses of headache, and found that drop out because of headaches was not conditional on whether the study drug was effective or not. In other words, there is no difference between those who remained in the study despite their headaches and those that chose to quit because of headaches. Moreover, they said that there appeared to be no relationship between dropping out of the study based on severity of headache. Nevertheless, a LOCF imputation is being added for conservatism. The sponsor also noted that they believe there will be very few dropouts during the first 21 days of the study (the primary endpoint completion date).

Patient Follow-up

Dr. Throckmorton reiterated our desire for data on all dropouts and completers of the study. In addition, we would like the timing of other pain relieving treatments (e.g., Sitz baths, Botox injections) specified in the protocol. Cellegy said they would specify what other therapies the patients in the study are receiving but said that following dropouts would be difficult. Dr. Throckmorton stated that the information gleaned from dropouts who continue to fill out their pain assessment forms will be useful in understanding the value of pain assessment in this patient population and the effect of discontinuing nitroglycerin on the anal fissure pain profile even though it will not be part of the 21 day primary efficacy analysis. The sponsor said they would include a statement in the Informed Consent Form making patients consent to continue filling out their pain assessment forms if they drop out.

Inclusion Criteria

Cellegy asked if the differences in the inclusion criteria between this trial and the previous efficacy trial would affect the Agency's interpretation of the results of the trials. Dr. Throckmorton replied that the differences in inclusion criteria should not affect decisions about interpretability of the trial.

Timing of Measurements

Dr. Throckmorton said that we believe that the patient's assessment of pain relief should be done at trough (at the end of the dosing interval). Cellegy stated that their reasons for doing a bedtime (peak) pain assessment include:

- That the physiological effect of the drug is not triggered by contact of the drug with the fissure, but is an indirect effect. The drug supposedly is thought to act by relaxing anal smooth muscles and thus reducing the intra-anal pressure which in turn has a pain-relieving effect, especially during defecation.

- That pain assessment by the patient is the patient's recollection of pain relief over the previous 24 hours. Therefore, the pain assessment is, in essence, a 24 hour average of pain relief.
- Bedtime is a time of better patient compliance for filling out pain assessment forms.

Dr. Throckmorton asked if the sponsor had data collected from other trials or sources on the temporal pattern of pain relief after applying the ointment. The sponsor replied that they should be able to get this information from colorectal surgeons or patients enrolled in previous trials. Dr. Throckmorton said this data should be obtained prior to starting the trial and submitted to the Division for review. Provided that the sponsor was able to demonstrate that there was no acute effect of the application on pain, the current proposal by the sponsor would be acceptable.

Secondary Endpoint: Time to 50% improvement

Dr. O'Neill noted that the sponsor's definition of the secondary endpoint of time to 50% reduction of pain did not seem reasonable given the potential within subject day to day variability in the pain scale assessment and he asked the sponsor for further clarification. Cellegy replied that this endpoint would capture a patient who achieved a 50% or greater reduction from their own baseline score in pain at some point in the study; those patients that did not have a 50% reduction by 21 days would be considered a failure. Dr. O'Neill said this endpoint could be influenced by daily events, for example, by the use of Sitz baths in the study, and suggested that perhaps a 50% or greater reduction in pain measurement averaged over a several day period should be used instead to ensure a more uniform and statistically accurate analysis, particularly when pain measurements have large variabilities. In addition, the analysis for the secondary endpoint should consider adjustment for and/or analysis of the influence of other daily events (eg. Sitz bath) on the pain score. Dr. Temple suggested that a count be done of the number of patients who actually achieve a 50% reduction in pain for the secondary endpoint.

Blinding

Cellegy asked for clarification regarding the Agency's request for the investigator to ask the patient whether they were on placebo or drug during the study. Dr. Temple said our intent was to gain reassurance about the blinding. The sponsor said the trial will be blinded through 56 days and the investigator will ask the patient about blinding at the 21 day time-point in the trial.

Stratification at Baseline

Dr. Karkowsky suggested that the sponsor consider stratifying for severity of baseline symptoms when entering patients into the study. Cellegy said they would take Dr. Karkowsky's suggestion under advisement and would inform the Agency on what approach they plan to take.

Summary of Main Action Items

1. Cellegy will submit data on the time-course of pain relief after application of the nitroglycerin ointment. This data should be submitted to the Division before the trial begins.
2. The Agency suggested changes to the protocol for:
 - More complete follow-up of all patients who drop out of the study, especially with regard to the intensity of their anal pain.
 - Changing the definition of the secondary endpoint-Time to 50% improvement in pain relief.
 - Specification of the timing of Sitz baths, Botux injections and other pain relieving modalities a patient is receiving while in the study.
 - Consideration of stratification of severity of headache at baseline.

Minutes Preparation:

Edward Fromm

Concurrence Chair:

Robert Temple, M.D.

ef/2/6/03-2/19/03-2/20/03-2/25/03

Rd: JLawrence-2/10/03

JHung-2/10/03

AKarkowsky-2/10/03

SKoessel-2/12/03

RO'Neill-2/11/03

GChi-2/11/03

DThrockmorton-2/20/03

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/s/

Edward Fromm
2/27/03 08:42:07 AM



IND 45,326

Cellegy Pharmaceuticals, Inc.
Attention: Daniel L. Azarnoff, M.D, F.A.C.P.
349 Oyster Point Boulevard., Suite 200
South San Francisco, CA 94080

Dear Dr. Azarnoff:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cellegesic (nitroglycerin) ointment.

We also refer to your request dated September 16, 2002, received September 17, 2002, for a special clinical protocol assessment. The protocol is entitled CP 125 02-02-02, "*A Study to Determine the Effect of CP125 Ointment on the Pain Associated with a Chronic Anal Fissure*".

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions. As we have discussed, one additional trial convincingly demonstrating efficacy of your drug product containing nitroglycerin (called CP125 in the current protocol) in reducing the pain associated with anal chronic fissures would be sufficient to support the approval of this product for that indication. We have the following comments regarding the adequacy of the proposed trial and its adequacy to assess the clinical safety and efficacy of CP125 in this population.

Population

The enrollment criteria for this study are different from those used in the previous studies, most critically in further limiting the use of standard therapies for anal fissures (*e.g.*, psyllium and Sitz baths that were mandated in study NTG 00-02-01). In the current protocol, you allow patients who are on therapies to continue them, but it isn't clear whether this includes therapies for anal fissures (*e.g.*, stool softeners) and to what extent you believe such therapies will be used by the patients enrolled in the trial. We understand that you previously limited the use of laxatives and certain other OTC products, but rigid exclusion of all other therapies is unacceptable, as it limits the generalizability of this study and our ability to understand potential interactions better that might occur between therapies. You should clarify the use of other therapies for anal fissures as allowed in the current protocol or amend the protocol to allow a broader use of standard therapies.

Your inclusion criteria specify a visual analogue scale (VAS) baseline score of ≥ 25 but do not specify when the score is to be obtained (*e.g.*, on waking, following defecation). This is highly relevant to any observed treatment effects. Please clarify the timing of this measurement in relation to other activities and therapies (*e.g.*, bowel movements, Sitz baths).

Your use of a VAS baseline score as part of the inclusion criteria differs from the previous trials. While this inclusion criterion may be useful in the analysis of the results and may identify a population most likely to benefit from therapy, this will complicate comparisons of any observed effects between the studies you have conducted.

Blinding

The potential for unblinding as a result of the headaches associated with nitroglycerin has been discussed at length. While this issue does not preclude the use of a symptom-driven primary endpoint, and you have made provisions to limit unblinding, we request that you include forms to collect two additional pieces of data:

- 1) A questionnaire administered at the end of the trial to both the physicians and the patients (separately) to ask what treatment they think the patient received. Any patient who drops out of the study should similarly be given this questionnaire to fill out at the time of discontinuation.
- 2) Collection of the headache adverse events should include data on the timing of the onset and resolution of the headache relative to study drug administration.

Primary Endpoint

The proposed end point is the average pain severity as assessed by a VAS each night. A substantial effect of your drug to reduce the intensity of pain would support a finding of clinical efficacy this population. However, the specific question that is to be answered by the patient needs to be specified in the protocol. Without precise wording, some patients will focus on the worst pain during the day while other will focus on the average pain and still others will focus on their pain status at the time they complete the questionnaire. Similarly, the timing of the pain assessment relative to usual activities (*e.g.*, defecation, Sitz baths, drug administration) is likely to critically affect the patient's response. To avoid a potential interaction with study drug administration, the assessment of the VAS should be performed at the end of the inter-dosing interval. The protocol should clarify exactly the type of pain to be assessed, the timing of its collection relative to other therapies and activities, and specify the question to be used in the pain assessment. You should substantiate their decision as to what pain is most meaningful to this patient population (as reflected in the question asked).

The measurement of the primary endpoint after 21 days of study drug is acceptable, but an understanding of the use of your drug beyond 28 days (the duration you propose) is necessary to provide information as to the longer-term effects of its use, particularly for patients who have residual pain after 21 days. The study should follow patients through 8 weeks to provide such information. This duration, while short of the period typically required for assessment of analgesic efficacy, would be sufficient to describe the short-term effects of your drug in this population. Following the completion of the study, patients should continue to be followed for the need for surgical interventions, as an additional assessment of long-term outcomes.

Additional Endpoints and Clinical Information

Information on the following relevant clinical outcomes should be collected in all patients.

- 1) Need for other medical (*e.g.*, investigational botulinum toxin) and surgical interventions for anal fissures. All patients must be followed after completion from the trial (or discontinuation for whatever reasons), to assess the need for these interventions.
- 2) Timing of onset and resolution of headaches.
- 3) Timing and use of analgesics, including the use of narcotics.

Statistical Issues**Missing data**

We assume that the population to be used for the primary efficacy analysis is the intention to treat population, but the protocol does not adequately specify the handling of missing data. Your proposal should take into account the likelihood that the incidence of dropouts due to headache is likely to be higher in the group receiving NTG (resulting in informative censoring). Absent an agreed-upon analysis method to handle these drop-outs, our conservative analysis would be to treat all treatment patients who discontinue as worst outcomes, while treating all placebo patients as censored. Any alternative analysis plan for handling drop-out should be submitted to the Agency in writing.

Statistical Modeling and Analysis Plan

The proposal of experimenting with statistical models and mathematical transformations to optimize the data-model fit is of concern to us. If the best fitting model is not specified *a priori* and the data are explored to select such model, the problem of multiplicity in testing may arise. Also, the credibility of the findings may suffer especially when the final p-value from the analysis of some transformed endpoint, in the face of extensive data dredging, is borderline significant. We believe that such experimenting can be conducted on data from previously conducted studies and any proposed alterations to the analysis plan based on the data should be specified prospectively in detail. We have the following comments that should be addressed before you initiate the study, to minimize any confusion when analyzing the data:

- 1) While you have proposed a complex analysis of integrated pain over time as the primary analysis method, an alternative (and acceptable) analysis method would be to compare the average VAS score at the end of week three in the two treatment groups to establish a treatment effect. This would have the added benefit of being easier to describe in labeling as a clinical benefit of substance.
- 2) Should you choose to conduct the primary analysis of the data as you have proposed, the benefit at the end of 21 days may be correlated to baseline VAS score, such that those with severe pain have a greater potential for benefit than those with modest pain at baseline. The small size of the study makes detecting significant imbalances, including difference for pain intensity at baseline, problematic. Possible approaches include:
 - a) Stratifying subjects based on the severity of symptoms at baseline.
 - b) Limiting the enrollments to subjects whose symptom scale fall in a prespecified narrow range (we do not favor this approach).
 - c) Incorporate an appropriate covariate in the analysis based on symptoms at baseline.

- 3) Should you choose to conduct the primary analysis of the data as you have proposed, we also require additional clarification of the statistical model to be used.
- a) Your analytic plan proposes choosing between a linear and a quadratic mixed-effects model. How the choice is made must be described in detail, and 'inspection of the data' as you propose is unacceptably ambiguous. If a quadratic model is chosen as the basis for the primary analysis, your proposed 'treatment by linear week interaction' will be difficult to interpret, as the rate of change will not be constant between weeks. Unless a clear treatment effect is demonstrated, the trial will not be interpretable as showing clinical efficacy. You need to specify how the rate of change by week would be incorporated into your analysis plan should a quadratic model be chosen.
 - b) Similarly, the current analytic plan proposes the transformations of the data if normalization assumptions are violated, to improve the fit, to change the VAS versus time curve or the time scale (week), or to correct for normality of distribution.
 - (1) A clear definition of the test to be applied to assess the normality of the distribution should be stated. In this regard, you should clarify whether you believe VAS scoring is distributed normally in the study population (as you seem to imply in section 11.1), and justify your conclusion.
 - (2) Given that the average of pain intensity is the primary endpoint the mathematical process of transforming the VAS so that normality assumptions are valid would alter the interpretation of the study. It will be difficult to translate changes in the transformed pain intensity into changes in what the patient actually feels and perceives as pain.
 - c) The proposed sample size of 75 subjects per group was based on the assumption that a linear model will fit the data. You should provide a discussion of the impact on the power of the study with this sample size if the most appropriate model includes a quadratic term.

Case Report Forms and Diaries

- 1) The case report forms have not been submitted for review. It is, therefore, unclear what data will be captured during the study.
- 2) The use of diaries to capture the use of analgesics and pain scores has been criticized, as the scores reported may be influenced by previous reported measures when a diary system is used, and may be filled out at times distant from the reporting period. The central collection of such data by a blinded assessor on a daily basis is preferable.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our draft "*Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products*"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at <http://www.fda.gov/cder/guidance/index.htm>. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

IND 45,326

Page 5

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5332

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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this page is the manifestation of the electronic signature.**

/s/

Doug Throckmorton
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Minutes of a Meeting between Cellegy Pharmaceuticals and the FDA

Date: June 11, 2002
Applications: NDA 21-359
Cellegesic (nitroglycerin ointment)
Applicant: Cellegy Pharmaceuticals, Inc.
Subject: Clinical Development

FDA Participants:

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research
Douglas C. Throckmorton, M.D., HFD-110, Division Director, Cardio-Renal Drug Products
Anthony Proakis, Ph.D., HFD-110, Pharmacologist
James Hung, Ph.D., HFD-110, Statistician/Team Leader
Mr. Edward Fromm, HFD-110, Regulatory Health Project Manager

Cellegy Pharmaceuticals

Mr. K. Michael Forrest, CEO and President
Daniel Azarnoff, M.D., Senior Vice President, Regulatory and Medical Affairs
William Scharv, Ph.D., Vice President, Regulatory Affairs

(b) (4)

Background

Cellegy submitted a 505(b)(2) application for Cellegesic Ointment (0.2 and 0.4% nitroglycerin) intended for use as a self-administered treatment to be applied intraanally at the site of an anal fissure and indicated for relief of pain associated with chronic anal fissures. The total dose studied was 1.5 to 4.5 mg/day.

The Division on April 5 and 22, 2002 informed the sponsor, that because of deficiencies with the application, they would likely receive a not approvable letter by the April 26, 2002 action date. Cellegy formally withdrew their application on April 26, 2002. They have requested a meeting to discuss new analyses of the data and how to proceed with future development of the drug.

Meeting

Cellegy's Presentation

Cellegy opened the meeting with a presentation detailing clinical development of the drug to this point. The sponsor said that they believe that the drug is effective for pain relief of anal fissures as shown by studies NTG 98-02-01 and NTG 00-02-01. They noted the linear, mixed effects regression statistical method used for the first study (NTG 98-02-02) also showed nominal statistical significance through 3 weeks in the second study (NTG 00-02-01). When a quadratic term was added to the second study, statistical significance was achieved throughout the 56 days of the study. They noted, however, that the magnitude of treatment effect in the second trial, although statistically

significant, was not as large as the first trial. The sponsor theorized that sitz baths and fiber were required in the second study and not the first one and may have decreased the impact of treatment.

Cellegy presented new analyses that they believe show that the drug has even more of an effect on patients that have features of more severe anal fissures. They noted that approximately 50-60% of the study population had these features (e.g., Sentinal Pile).

Medical Consultants for Cellegy said that there was a need for a commercial nitroglycerin ointment product because of the overall incidence of the disease (about 700,000 cases/year), and the bleeding and pain associated with the anal fissures were debilitating to many patients. At the present time, however, nitroglycerin ointment can only be obtained by extemporaneously compounding it by pharmacies. The problem with the current setup is that the extemporaneously compounded nitroglycerin preparations are potentially less homogeneous and there are no uniform dosing information for patients. Nevertheless, they have noticed pain relief with patients treated with these preparations and asserted that this treatment sometimes prevents expensive surgeries.

The sponsor presented a slide showing that there was no association between headache and anal fissure pain when using the nitroglycerin ointment. They noted that their experience shows that headaches reported by patients tend to be transient and dissipate over a very short period of time, although they have no collected data on this. Moreover, they theorize that a least some of the patients who dropped out of the study due to headache did so after achieving pain relief and therefore these patients may have concluded that there was no reason to continue using the drug. Cellegy noted that the incidence of headache with their product is no greater than the commercially available nitroglycerin preparations and therefore could be covered in the labeling like these products.

Agency's Response

Statistical Analysis

Dr. Temple said we are primarily concerned that the statistical analysis used for the first trial was not applied to the results of the second study. Although a quadratic term may be the best "fit" for the curvilinear results of the second trial, this method was not prespecified and, in a sense, undermines the replication of results needed for approval of the drug. In addition, the p value for the second trial, although statistically significant, was not as robust as the Agency would have liked. Cellegy argued that their protocol gave them room to make adjustments for differential rates of change and therefore they did not believe that they were changing statistical analyses after the fact to ensure the best result. Dr. Temple said the sponsor should review how the statistical analyses were determined for each study and submit a presentation detailing why it was reasonable not to prespecify unambiguously the statistical method for the second trial.

Next Trial

Dr. Temple said, short of convincing us that the statistical plan used for the second trial was reasonable, another trial would be necessary to gain approval. This trial should be long-term but could have a primary endpoint at the end of 2-3 weeks of therapy.

Cellegy asked if the trial could focus specifically on a subset of patients with anal fissure (e.g., those with Sentinal Piles). Dr. Temple said that it would probably be acceptable, but a case would need to be made that we could as extrapolate information from these patients to the overall population for that disease state. The data from the two earlier trials would aid in this.

The sponsor asked if they should specify the standards of care for the next trial. Dr. Temple said they could specify the standards of care, but noted that the use of sitz baths and fiber in the placebo group in the second trial did not appear to have a treatment effect in that group.

Headache

Dr. Throckmorton noted that about a third of the patients receiving the drug experienced some degree of headache for more than 5 days. Dr. Temple said he believes the occurrence of headaches can be covered in the labeling, but suggested that in the next trial the sponsor try to establish a clearer temporal relationship between drug use and the frequency and severity of headaches.

Global Assessment Scale

Dr. Throckmorton said the sponsor should consider an assessment scale for the next trial that would quantify the patient's perception of headache compared to the relief of their anal fissure pain. We realize the limitations of this type of survey but it could be helpful in determining the overall efficacy of the drug.

LidaMantle and LidaMantle HC

Cellegy asked what the approval basis was for the claim of anal fissure pain for LidaMantle and LidaMantle HC. Dr. Temple replied that we would have to check with the Division of Dermatologic and Dental Drug Products for this information but said it was his impression that these claims were of general sort common to topical anesthetic products. Dr. Throckmorton requested that the package inserts for the LidaMantle HC and Analpram HC be sent to his attention for review.

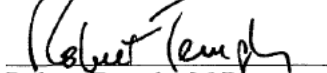
Summary of Main Action Items

- Cellegy will submit a rationale for the statistical methodology used for the first and second trial. The Agency will try to obtain the basis of approval for the indications listed for LidaMantle, LidaMantle HC, and Analpram HC. The sponsor will send the package inserts for the LidaMantle HC and Analpram HC products to the Division for review.

Minutes Preparation:


Edward Fromm

Concurrence Chair:


Robert Temple, M.D.

ef/6-11-02/6-17-02/6-27-02

Rd: AProakis-6/11/02
JHung-6/13/02
DThrockmorton-6/14/02



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-359

Cellegy Pharmaceuticals Inc.
Attention: Mr. K. Michael Forrest
Chairman, President & CEO
349 Oyster Point Blvd., Suite 200
South San Francisco, CA 94080

Dear Mr. Forrest:

We received your April 25, 2002 correspondence on April 25, 2002 notifying us that you are withdrawing your unapproved new drug application (NDA) for Cellegesic (nitroglycerin ointment). This application was filed on August 25, 2001.

In accordance with 21 CFR 314.65, this application is withdrawn as of April 25, 2002. This withdrawal does not prejudice refiling of this application. You may reference information contained in this withdrawn application in any future submission.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5313

Sincerely yours,

Natalia A. Morgenstern
Chief, Project Management Staff
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/

Natalia Morgenstern
5/7/02 04:54:42 PM

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
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Transmitted to FAX Number: (650) 616-2222

Attention: Dr. Daniel Azarnoff

Company Name: Cellegy Pharmaceuticals

Phone: (650) 616-2214

Subject: **Information Requests from Dr. William Timmer,
Review Chemist for NDA 21-359
Cellegesic (nitroglycerin) Ointment**

Date: May 3, 2002

Pages including this sheet: 2

From: Edward Fromm

Phone: 301-594-5313

Fax: 301-594-5494

INFORMATION REQUESTS:

1. Please explain the rationale of including (b) (4)% (b) (4) in the 0.2% formulation but not in the 0.4% formulation.
2. Please state the retest date for the drug substance?
3. Regarding test (b) (4)-0038-LC: Quantitative analysis of known impurities in nitroglycerin ointment: currently, the impurities are reported with no acceptance criteria. Please develop a limit for each impurity and a total impurity limit. This applies to impurity testing for the drug substance, release testing after manufacture of the ointment, and stability of the drug product.

One set of all encompassing physico-chemical tests should be developed for the finished dosage form to function as regulatory specifications as well as stability specifications. These specifications should be developed to validate the identity, strength, quality, potency and purity of the finished drug product. Accordingly, the tests should include an assay that reports percentage of the drug substance as well as impurities/degradation products.

4. Please develop a numerical acceptance criterion for the viscosity test, which is part of the stability program.

Minutes of a Telecon between Cellegy Pharmaceuticals and the FDA

Date: April 24, 2002

Applications: NDA 21-359
Cellegesic (nitroglycerin ointment)

Applicant: Cellegy Pharmaceuticals, Inc.

Subject: Issues regarding Approvability

FDA Participants:

Douglas C. Throckmorton, M.D., HFD-110, Division Director, Cardio-Renal Drug Products
Ms. Natalia A. Morgenstern, HFD-110, Chief, Project Management Staff
Mr. Edward Fromm, HFD-110, Regulatory Health Project Manager

Cellegy Pharmaceuticals

Mr. K. Michael Forrest, CEO and President
William Schary, Ph.D., Vice President, Regulatory Affairs

Background

Cellegy has submitted a 505(b)(2) application for Cellegesic Ointment (0.2 and 0.4% nitroglycerin) intended for use as a self-administered treatment to be applied intraanally at the site of an anal fissure and indicated for relief of pain associated with chronic anal fissures. The total dose studied was 1.5 to 4.5 mg/day.

The sponsor requested a telecon to discuss follow-up questions arising from the April 22, 2002 meeting with the Division in which they were notified that a not approvable action will be taken unless the sponsor decides to withdraw the application before the April 26, 2002 goal date.

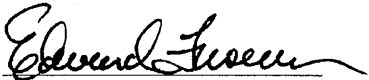
Telecon

Cellegy opened the telecon by asking for clarification about the Division's comments at the last meeting in which investigator unblinding due to nitroglycerin induced headache was raised as an issue. The sponsor noted that headache is a well-know side effect of nitroglycerin use and therefore it would seem that it would be nearly impossible to conduct a trial that would lead to approval. They also noted that they prefer to have pain as the primary end point in a future trial and asked if this was acceptable.

Dr. Throckmorton replied that pain is an acceptable endpoint, but an effect on it by nitroglycerin ointment has not been demonstrated in the trials to date. He noted that the sponsor should measure other outcomes (e.g., Quality of Life, effects on healing, pharmacodynamic effects) so that the consistency and totality of the data in the next trial would be sufficient to demonstrate efficacy. The sponsor asked about the issue of unblinding due to the headaches. Dr. Throckmorton said that while it was an issue, in the context of the review for the application, unblinding was not considered a major deficiency. The Agency would meet with the sponsor promptly to discuss additional trial details if that would be useful.

Cellegy said they are leaning toward withdrawing the application before the goal date and asked if they could receive a list of deficiencies of the application. Dr. Throckmorton said that the clinical/statistical deficiencies

ould be conveyed through the minutes of the meeting held on April 22, 2002. The chemistry and otopharmaceutics deficiencies will be sent to the sponsor shortly. Dr. Throckmorton said the sponsor should be aware that by receiving a not approvable letter they retain their right to appeal our action. Cellegy thanked Dr. Throckmorton for this information but said they will likely withdraw the application prior to the goal date.

Minutes Preparation: 
Edward Fromm

Concurrence Chair: 
Douglas C. Throckmorton, M.D.

ef/5-6-02/5-10-02

Rd: NMorgenstern-5-7-02

Minutes of a Meeting between Cellegy Pharmaceuticals and the FDA

Date: April 22, 2002

Applications: NDA 21-359
Cellegesic (nitroglycerin ointment)

Applicant: Cellegy Pharmaceuticals, Inc.

Subject: Issues regarding Approvability

FDA Participants:

Douglas C. Throckmorton, M.D., HFD-110, Division Director, Cardio-Renal Drug Products
Stephen Fredd, M.D., HFD-110, Deputy Division Director of Policy
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Kasturi Srinivasachar, Ph.D., HFD-810, Team Leader, Division of New Drug Chemistry I
Anthony Proakis, Ph.D., HFD-110, Pharmacologist
James Hung, Ph.D., HFD-110, Statistician/Team Leader
Nhi Nguyen, Pharm.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Ms. Denise Hinton, HFD-110, Regulatory Health Project Manager
Mr. Edward Fromm, HFD-110, Regulatory Health Project Manager

Cellegy Pharmaceuticals

Mr. K. Michael Forrest, CEO and President
Daniel Azarnoff, M.D., Senior Vice President, Regulatory and Medical Affairs
William Schary, Ph.D., Vice President, Regulatory Affairs

(b) (4)



Background

Cellegy has submitted a 505(b)(2) application for Cellegesic Ointment (0.2 and 0.4% nitroglycerin) intended for use as a self-administered treatment to be applied intraanally at the site of an anal fissure and indicated for relief of pain associated with chronic anal fissures. The total dose studied was 1.5 to 4.5 mg/day.

The sponsor was informed in a telecon on April 5, 2002, that because of deficiencies with the application, it would likely receive a not approvable letter by the April 26, 2002 action date. Cellegy requested a meeting to discuss the deficiencies enumerated at the April 5, 2002 telecon as well as to discuss new analyses of the data that they believe confirm the effectiveness of the drug in treating pain associated with anal fissures.

Meeting

Cellegy's Presentation

Cellegy opened the meeting with a presentation detailing the disease course of anal fissures and how extemporaneously compounded nitroglycerin ointment has, in their opinion, been used to successfully treat pain from anal fissures and possibly avoid surgery. They noted, however, that the extemporaneously compounded nitroglycerin preparations are likely not homogeneous and there are no uniform dosing information for patients.

The sponsor said that they believe that the drug is effective for pain relief of anal fissures as shown by both studies, NTG 98-02-01 and NTG 00-02-01. They noted the linear regression statistical analysis used for the first study (NTG 98-02-02) also showed statistical significance for up to 3 weeks in the second study (NTG 00-02-01). When a quadratic term was added to the second study, statistical significance was achieved throughout the 56 days of the study. They also noted that the pain relief results of the first study are enhanced when a quadratic term is used in the statistical analysis of the results. Dr. Fredd asked how dropouts were handled when doing the statistical analyses for the studies. The sponsor said that in the mixed regression analyses, the dropouts were censored.

Cellegy presented slides of a recent analysis that they did that showed a LOCF (Last Observation Carried Forward) comparison of 50% pain relief (time to 50% reduction in pain relief) in the two studies individually, and as a combined result. In each of the studies and when the results were combined, the sponsor noted that a positive, statistically significant result was achieved. They pointed out that they believe this analysis is meaningful because patients can easily discern between having pain and having 50% less pain. Dr. Fredd asked if the drug was beneficial why did not the QOL (Quality of Life) assessment show that patients experienced improvement when treated with the drug. The sponsor replied that they believe that the QOL assessment was not designed appropriately with respect to pain relief reduction and how it affects QOL but noted that the assessment would certainly be modified for any future trials.

The sponsor presented a slide showing that there was no association between headache and anal fissure pain when using the nitroglycerin ointment. They explained that 7 out of the 8 patients that dropped out of the study due to headaches said that their pain level was 0 when they left the study. Dr. Fredd said that it was his analysis, based on the CRFs (Case Report Forms), that more patients left the study because of nitroglycerin-induced headache. The sponsor acknowledged that some patients acquired a headache while receiving the drug in the study, but noted that this could be covered in the labeling like the other nitrates currently being marketed.

Summary of Clinical/Statistical Deficiencies of the Application

Dr. Throckmorton said that we agree with the sponsor that the nitroglycerin ointment should be uniformly compounded and that surgical interventions should be avoided. He said, however, that because of clinical/statistical deficiencies the application is not approvable. They are as follows:

- The two pivotal studies failed to demonstrate a significant effect of the drug on their pre-specified end points of anal fissure healing (NTG 98-02-01) and reduction of anal fissure pain (NTG 00-02-01). Literature references supplied by the sponsor indicate that either of the trials should have easily been able to detect a robust result on either of the two primary end points. Dr. Throckmorton said that it appeared that a secondary end point of the first trial, pain reduction, was positive when the drug was given at high doses. Correctly, the sponsor

conducted a second trial that had reduction in pain as the primary, pre-specified end point. However, when the regression analysis used in the first trial was applied to the data from study NTG 00-02-01, no significant effect of the drug on anal pain was demonstrated. While there may be an effect of the drug during the first one to two weeks of therapy, this finding is difficult to interpret because the pre-specified duration of the trial was 56 days. The sponsor noted that they used a quadratic model in the statistical analysis of the second study because it offered the best way of measuring the differential rate of change generated by the data from this study. They also noted that they chose a duration of 56 days because they believe that drug exerts a healing effect beyond the time needed to achieve pain relief.

- Any suggestion of pain relief is mitigated by the increase incidence of both severe headaches and headaches leading to withdrawal in the drug groups compared with placebo. It is also possible that investigators were “unblinded” in the study due to these headaches.
- A QOL assessment appeared to show no benefit to those patients who received nitroglycerin ointment compared to placebo.
- There were no trends in either study that suggested an improvement of healing of anal fissures.
- There was an absence of follow-up data from patients in the study to see if those patients that were treated with the drug experienced fewer surgeries compared to those patients that were on placebo.

Possible Remedies

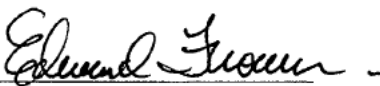
Dr. Throckmorton said that additional information and/or analyses would be needed before the drug could be approved. They are as follows:

- Conduct a trial of a shorter duration (2 to 3 weeks) because this seems (from your consultants) the time of greatest pain relief when using the extemporaneously compounded nitroglycerin ointment. Dr. Fredd suggested that the effect of the drug may be more pronounced in a study that uses patients that describe their anal pain as “debilitating”. He noted that patients that were successfully treated in the short-term study could be randomly withdrawn after completion to see what the rate of exacerbation was between the two groups.
- Follow-up data from patients on the studies completed and those in the future should be collected to see if there is a higher rate of surgeries between those receiving the ointment and those on placebo.
- A QOL/Activities of Daily Living assessment should be done to show that patients feel better even though some are experiencing headaches.
- Measures of the pharmacodynamic effect of the drug, such as anal sphincter pressure information would be useful and could demonstrate that tachyphylaxis does not occur with the drug. The sponsor noted that the doses of the drug given in the studies were separated by 12 hours and therefore do not believe that tachyphylaxis develops over time.

Conclusion

Dr. Throckmorton noted that the application would receive a not approvable action by the April 26, 2002 goal date, unless the sponsor decides to withdraw their application by that date. He said that the hypothesis generated in the first trial of pain relief of anal fissures was not confirmed by the second study. Other supporting evidence such as the QOL assessment and healing of fissures were not found in the second study. Furthermore, headaches, sometimes severe, caused patients to dropout from the study at a much higher rate than placebo.

A new trial and/or additional analyses will be needed before the drug can be approved. The Division would be happy to meet with the sponsor in the future to help address the identified deficiencies.

Minutes Preparation: 
Edward Fromm

Concurrence Chair: 
Douglas C. Throckmorton, M.D.

ef/4-29-02/5-03-02

Rd: DHinton-4-29-02
KSrinivasachar-4-30-02
NNguyen-5-01-02
AProakis-5-01-02
JHung-5-02-02
NStockbridge-5-01-02
SFredd-5-02-02
DThrockmorton-5-02-02

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Minutes of a Telecon between Cellegy Pharmaceuticals and the FDA

Date: April 5, 2002

Applications: NDA 21-359
Cellegesic (nitroglycerin ointment)

Applicant: Cellegy Pharmaceuticals, Inc.

Subject: Issues regarding Approvability

FDA Participants:

Douglas C. Throckmorton, M.D., HFD-110, Division Director, Cardio-Renal Drug Products
Stephen Fredd, M.D., HFD-110, Deputy Division Director of Policy
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
William Timmer, Ph.D., HFD-810, Review Chemist
Nhi Nguyen, Pharm.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Ms. Natalia A. Morgenstern, HFD-110, Chief, Project Management Staff
Mr. Edward Fromm, HFD-110, Regulatory Health Project Manager

Cellegy Pharmaceuticals

Mr. K. Michael Forrest, CEO and President
Daniel Azarnoff, M.D., Senior Vice President, Regulatory and Medical Affairs
Mr. John Chandler, Vice President, Corporate Development
Mr. Robert Janosky, Director, Marketing
Mr. Richard Juelis, CFO and Vice President, Finance
JC Lee, Ph.D., Vice President, Development
Vivien Mak, Ph.D., Vice President, Research
Mr. Michael Miller, Vice President, Commercial Development
Mr. Sujata Sankar, Director, Clinical Operations
William Schary, Ph.D., Vice President, Regulatory Affairs

Background

Cellegy has submitted a 505(b)(2) application for Cellegesic Ointment (0.2 and 0.4% nitroglycerin) intended for use as a self-administered treatment to be applied intraanally at the site of an anal fissure and indicated for relief of pain associated with chronic anal fissures. The total dose studied was 1.5 to 4.5 mg/day.

The Division requested a telecon with the firm to discuss issues related to the approvability of the drug since the primary goal date (April 26, 2002) for the application is approaching.

Telecon

Dr. Throckmorton opened the telecon by noting that he has looked at the reviews for the application, and unfortunately concluded that the application is not approvable. Some of our reasons for this decision are outlined below:

Study NTG 98-02-01

This study proposed an effect on healing but was unable to show this result. However, a secondary, pre-specified endpoint of pain relief did have a nominal, statistically positive effect over time using a mixed effects model, and this generated a hypothesis, i.e., that NTG ointment could relieve anal pain associated with chronic anal fissures without healing them. To test that hypothesis prospectively a second study (NTG 00-02-01) was performed.

Study NTG 00-02-01

This study had as its primary endpoint pain relief rather than healing of anal fissures. When we used the statistical analysis method employed for the first study in the mixed effects model, we failed to find a statistically significant effect. We noted that the firm had elected to use a different statistical method employing a quadratic term (rather than a linear term as per the initial study) that seemed to indicate an effect of the drug at week 1 or 2 but not over time for the duration of the study. Dr. Throckmorton noted that the reviewers conducted sub-analyses of their own which looked at the effect of the drug on pain described as “worst pain” and defecation pain. There did not appear to be any greater effect compared to “average pain.”

Another sub-analysis that we performed was to see how frequently patient’s pain was completely relieved (0%) at the end of the treatment period. This type of analysis is beneficial in that it is easy for us to determine, in an unequivocal way, the clinical benefit of the drug. Although there appeared to be some numerical trend when using this analysis in the first (NTG 98-02-01) trial, the effect was not replicated in the second trial. Additionally a LOCF analysis was done which showed no benefit.

Dr. Throckmorton noted that the second trial had a Quality of Life assessment that was not favorable. He also added that anal fissure healing, although not a primary endpoint of the second study, was null as it had been in the first study.

Safety

Dr. Throckmorton said a major side effect of the drug is headache, which in a sense, may offset any apparent rectal pain relief from the drug.

Biopharmaceutics

Dr. Nguyen asked that the sponsor submit the full validation assay information for the PK study.

Conclusion

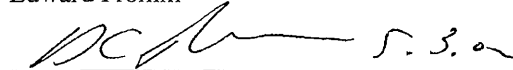
Dr. Throckmorton noted that the suggestion of an effect on anal pain in the first trial was not replicated in the second trial. Therefore a not approvable action was likely and additional clinical data will be needed before the drug can be approved.

The Division will be happy to discuss any analyses it has done of the present data as well as discuss a new trial(s) that would be sufficient to support approval in the future. Cellegy said they will discuss the Division’s comments today internally and will be in contact with the Division as to how they wish to proceed with the application.

Minutes Preparation:


Edward Fromm

Concurrence Chair:


Douglas C. Throckmorton, M.D.

ef/4-10-02/4-19-02/5-2-02

Rd: WTimmer-4-10-02
NNguyen-4-10-02
NStockbridge-4-10-02
SFredd-4-12-02
DThrockmorton-4-14-02
NMorgenstern-5-2-02

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

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Transmitted to FAX Number: (650) 616-2222

Attention: Dr. William Schary

Company Name: Cellegy Pharmaceuticals

Phone: (650) 616-2215

Subject: **Dr. Hung's Request for Additional Information for
NDA 21-359
Anogesic (nitroglycerin) Ointment**

Date: January 14, 2002

Pages including this sheet:

From: Edward Fromm

Phone: 301-594-5313

Fax: 301-594-5494

Bill,

Dr. Hung requests the following information:

For the Study NTG 00-02-01, the protocol states that the primary hypothesis is tested via the treatment by week interaction (i.e., the rate of change in pain is different between active treated and vehicle treated subjects). This statement seems to indicate that linear model in week would be used. No model was specified in the proposed mixed-effect analysis in the protocol. In the Statistical Document (Appendix 2), the pain data were evaluated in two ways. First, examined daily pain data over 56 study days. Second, evaluated mean weekly pain by taking the mean of the individual daily pain ratings for each week. Then, it went on to explain the model. The model for the PRIMARY mixed-effect analysis appeared to contain center,

day (linear and quadratic), tx, and tx by day (linear and quadratic) interaction. Only intercepts and slopes are random and the unstructured residual covariance matrix was used in the PRIMARY analysis.

1) Was WEEK or DAYS used in the primary mixed-effect analysis? If DAYS was used, the residual covariance matrix will have 1596 parameters.

2) Request for the computer output of the primary mixed-effect analysis using MIXREG program or SAS PROC MIXED program.

3) Request for SAS data sets that contain reason for occurrence of missing values and demographic data.

Thank you,

Ed

Filing Summary

Meeting Date: August 15, 2001
Sponsor: Cellegy Pharmaceuticals, Inc.
Drug: Anogesic® (0.2 and 0.4% Nitroglycerin Ointment)
NDA Number: 21-359
Meeting Chair: Douglas Throckmorton, MD
Meeting Recorder: John Guzman
Participants:

FDA

Douglas Throckmorton, MD	Deputy Director, Division of Cardio Renal Drug Products, HFD-110
Stephen Fredd, MD	Deputy Director, Division of Cardio Renal Drug Products, HFD-110
Charles Resnick, PhD	Team Leader, Pharmacology, HFD-110
Anthony Proakis, PhD	Pharmacologist, HFD-110
Kasturi Srinivasachar, PhD	Team Leader, Division of New Drug Chemistry, HFD-810
James Hung, PhD	Team Leader, Statistical, Division of Biometrics I, HFD-710
Nhi Nguyen, PharmD	Clinical Pharmacologist and Biopharmacist, HFD-860
John Guzman	Regulatory Health Project Manager, HFD-110

Background

Cellegy has submitted a new 505(b)2 NDA (NDA 21-359) for Anogesic® Ointment (0.2 and 0.4% nitroglycerin) intended for use as a self-administered treatment to be applied intraanally at the site of an anal fissure and indicated for relief of pain associated with chronic anal fissures. The total proposed dose for Anogesic® is 1.5 to 4.5 mg/day.

Submission Information

Therapeutic Classification:	3S
Date of Application:	June 22, 2001
Date of Receipt:	June 26, 2001
10-Month User Fee Goal Date:	April 26, 2002
12-Month User Fee Goal Date:	June 26, 2002
User Fee Status:	Paid
Submission Complete As Required by 21 CFR 314.50?	Yes
Patent Information Included?	Yes
Exclusivity Requested?	No
Debarment Statement Included?	Yes
Financial Disclosure Certification?	Yes
Pediatric Rule Addressed?	Yes (requested deferment in submission)

Assigned Reviewers

<u>Discipline</u>	<u>Reviewer</u>	<u>Review Completion Date</u>
Medical	Stephen Fredd, MD	March 1, 2002
Biostatistics	James Hung, PhD	March 1, 2002
Chemistry	William Timmer, PhD	December 28, 2001
Pharmacology	Anthony Proakis, PhD	February 1, 2002
Biopharmaceutics	Nhi Nguyen, PharmD	November 30, 2001
Project Management	John Guzman	TBA

Other Issues

- The submission is not complete. Daniel Azarnoff, MD from Cellegy indicated that data from their ongoing pain relief study would not be submitted till December, 2001.
- The data from the completed pivotal study # NTG 98-02-01 is confusing (negative baseline values, etc) and appears suspect. Both Dr. Fredd and Dr. Hung would like the Sponsor to submit all CRFs for that study, and would like to make sure that the Sponsor submits all the CRFs for the study to submitted in December 2001.
- OPDRA does not approve of the tradename "Anogesic" as it could be confused with "Analgesic" and "Argesic" and is "too fanciful" a name for drug that is a common substance.

Signature, Meeting Recorder: See appended electronic signature page John Guzman

Signature, Meeting Chair: See appended electronic signature page Douglas Throckmorton, MD

Drafted: August 21, 2001
Reviewed: Nguyen 8/22/01
Hung 8/22/01
Srinivasachar 8/22/01
Proakis 8/22/01
Resnick 8/22/01
Fredd 8/22/01
Throckmorton 8/22/01

Cc: HFD-110
HFD-110/Guzman

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/s/

John Guzman

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NDA 21-359

Cellegy Pharmaceuticals, Inc.
Attention: Daniel L. Azarnoff, M.D.
349 Oyster Point Boulevard, Ste 200
South San Francisco, CA 94080-1913

Dear Dr. Azarnoff:

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: Anogesic® Ointment 0.2%/0.4% (nitroglycerin ointment)

Review Priority Classification: Standard (S)

Date of Application: June 22, 2001

Date of Receipt: June 26, 2001

Our Reference Number: NDA 21-359

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 25, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 26, 2002 and the secondary user fee goal date will be June 26, 2002.

Be advised that, as of April 1, 1999, 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 (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application.

In no case, however, will the determination be made later than the date action is taken on the

application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed 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
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: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, please call:

NDA 21-359
Page 3

Mr. John Guzman
Regulatory Health Project Manager
(301) 594-5312

Sincerely,

{See appended electronic signature page}

Natalia A. Morgenstern
Chief, Project Management Staff
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/

Natalia Morgenstern
7/12/01 06:04:40 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 27, 2001
TO: NDA 21-359 File
FROM: John Guzman (RPHM - Div of Cardio-Renal - HFD-110)
SUBJECT: **Telecon on September 7, 2001**
NDA 21-359 – Anogesic Ointment

A brief telecon was conducted between William Schary, VP of Regulatory Affairs at Cellegy Pharmaceuticals, and Dr. Stephen Fredd (Deputy Director, HFD-110) and myself. Dr. Fredd wanted to communicate to the Sponsor that the review of the clinical portion of NDA 21-359 had been difficult to this point due to the lack of data and inadequate data presentation in the submission. Dr. Fredd requested the following from Cellegy:

- All the CRFs for every patient in each of the pivotal studies (the one submitted with the NDA and the one to be submitted in December of 2001);
- Listing of all patients that withdrew from the studies, and how those patients were included in the analysis;
- An explanation of the “negative” pain scores that were recorded for certain patients;
- Demographic data for each group, and subgroup analysis for each randomized group;
- For the “rectal pain” claim, the Division needs expanded info on the anal pain scores – How was the data transposed from the diaries to the CRF?

It was also noted that the analysis made no attempt at answering the question of the secondary endpoints. Dr. Fredd informed the Sponsor that he and Dr. Hung would review the proposed statistical analysis of the study to be submitted in December 2001, and will communicate any comments/suggestions that he feels are important.

John Guzman

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/s/

John Guzman
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CSO

Minutes of a Meeting between Cellegy Pharmaceuticals and the FDA

Date: January 12, 2001

Applications: IND 45,326
Anogesic (nitroglycerin ointment)

Applicant: Cellegy Pharmaceuticals, Inc.

Subject: Guidance on clinical development

FDA Participants:

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Emmanuel Fadiran, Ph.D., HFD-860, Clinical Pharmacologist/Biopharmaceuticist
John Lawrence, Ph.D., HFD-110, Statistician
Edward Fromm, HFD-110, Project Manager
Quynh Nguyen, Pharm.D., HFD-110, Project Manager
Daryl Allis, HFD-110, Project Manager
John Guzman, HFD-110, Project Manager

Cellegy Pharmaceuticals

Daniel Azarnoff, M.D., Senior Vice President, Clinical and Regulatory Affairs
Andrew Korey, Ph.D., Vice President, Clinical Research

(b) (4)

K. Michael Forrest, Chairman, Board of Directors, CEO and President

Background

Cellegy Pharmaceuticals met with the Division in December, 1999 to discuss clinical development of nitroglycerin ointment after a pivotal phase 3 trial showed disappointing results with regard to the primary endpoint, healing of anal fissures. The sponsor believed, however, that there was statistically significant improvement in the secondary endpoint, pain relief with the 0.2% and 0.4% preparations, and asked the Division if a new trial could be launched with pain relief as the primary endpoint. The Division said a new trial with pain relief as the primary endpoint was acceptable, although it said a trial with more (higher) doses would be more informative.

Cellegy requested a meeting with the Division because they were having difficulty enrolling subjects for the new (pain relief) trial and asked if results from the first trial, clinical trial data from a similar Australian approved product, Rectogesic, and published literature could support approval of a NDA for Anogesic Ointment.

Meeting

The firm opened the meeting by stating that a trial using nitroglycerin ointment for the treatment of pain relief was experiencing recruitment problems (due, in some cases, to the availability of an extemporaneously compounded ointment) and asked if data from the first trial, clinical trial data

from a similar Australian approved product, and published literature could support approval of a NDA for Anogesic Ointment. They noted that they believed that the extemporaneously compounded product was being used inappropriately and not being manufactured according to GMP standards. Dr. Lipicky responded by saying that without another trial showing convincing evidence of pain relief with their formulation, the Division's recommendation would be non-approval of the product.

Cellegy asked if they could send in the results of clinical data in now as part of an NDA submission and then later in the review process send the results of the pain relief trial, provided, of course, that they are positive. Dr. Lipicky said that if the firm sent in a NDA submission, he would not "refuse to file" the application, but noted that a "rolling submission" as the firm proposes is not an ideal one for the Division as it makes management of resources more difficult. He said that if the firm sent in the pain relief results later in the review process it also might be necessary to extend the review clock by up to 3 months. Dr. Lipicky noted that if the firm decides not to send in a NDA application at this time, he would be open to issuing a "information request" letter stating what would be needed for approval of the product.

Trial Modifications

The firm noted that their current protocol uses 2 doses of nitroglycerin ointment and placebo; they asked the Division if they could drop the placebo arm and do a dose response trial. Dr. Lipicky said that they could but ideally the firm should study more doses and show a non-zero slope. Dr. Stockbridge noted that if the placebo arm is not contributing to the recruitment problem it should not be dropped. The sponsor affirmed that they believe that their recruitment difficulties are primarily the result of the extemporaneous nitroglycerin products and not the presence of a placebo arm in the study.

Site enrollment

The sponsor asked if it was a problem for the Division if a large number of patients were enrolled from one site (e.g., Israel). Dr. Lipicky said the Division did not object to the sponsor enrolling the majority of patients needed for the study from one site. He said the Division was also comfortable with the sponsor enrolling a few patients from many centers.

Interim Look

Cellegy asked the Division if they could take an interim look at the data collected so far to see what the effect size is. Dr. Lipicky said they could but that they would have to prespecify the interim look to the Division before attempting it; he noted that the firm would have to spend some alpha (.01 to .02) as a penalty for doing this. The details of this should be outlined in the form of a protocol amendment to the Division. Dr. Lipicky also noted that the firm would have to increase the sample size to compensate for this interim look or risk losing power.

The firm asked the Division if there was a preferred method of taking an interim look. Dr. Lawrence said that there were several common methods (e.g., O'Brien-Fleming or Pocock boundaries) that could be employed for this purpose. The Division does not have a preference provided that the overall type I error rate is maintained at 5%.

Pharmacokinetics

Dr. Lipicky asked the firm if it had collected blood samples for nitroglycerin in the patients studied to date. The firm said that it had conducted both single and multiple dose PK studies in healthy human volunteers.

Tolerance Development

Dr. Lipicky asked the sponsor what the time-course was for the disappearance of headaches associated with use of the nitroglycerin ointment. The firm said that the headaches tend to go away after several days of treatment with the nitroglycerin ointment. Dr. Lipicky expressed concern that tolerance was developing to the healing effect of the drug as evidenced by the sponsor's first trial that used nitroglycerin for 2 months but failed to produce a significant healing of anal fissures. The firm disagreed, saying that tolerance develops to the vascular effects (headaches) of the drug but that the literature supports the association of increased healing of anal fissures with increased duration of use of the nitroglycerin product. They added that the 2 months duration of use chosen for the first trial was due to evidence that anal fissures are difficult to heal and that study analyses required that timeframe to compensate for dropouts. Dr. Lipicky said an important consideration for the Division would be how to include in the package insert dosing information and instructions for use for the nitroglycerin ointment; he said it seems unreasonable to prescribe the ointment for 2 months (for pain relief) and therefore the firm would need to justify any duration of use for the product with data from the ongoing (pain relief) trial.

Conclusion

Dr. Lipicky told the firm that the results from the first trial, clinical trial data from a similar product in Australia, and published literature would not be a sufficient basis of approval of a NDA for Anogesic Ointment. He said the firm would need convincing results from their ongoing pain relief trial and would also need to address the potential development of tolerance to the ointment as well as how long the product will be prescribed for in the treatment of pain relief for anal fissures.

Minutes Preparation:

Edward Fromm

Concurrence Chair:

Raymond Lipicky, M.D.

ef/1-17-01/01-23-01

Rd: QNguyen-1/19/01
JGuzman-1/23/01
EFadiran-1/23/01
JLawrence-1/23/01
NStockbridge-1/23/01

cc: IND 45,326

/s/

Edward Fromm

1/25/01 06:37:16 PM

Dr. Lipikcy signed the minutes on Jan. 24, 2001

Minutes of a Meeting between Cellegy Pharmaceuticals and the FDA

Date: December 7, 1999

Applications: IND 45,326
Anogestic (nitroglycerin ointment) 0.1%, 0.2%, 0.4%

Applicant: Cellegy Pharmaceuticals, Inc.

Subject: Clinical trial results and guidance on future trial design

FDA Participants:

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Robert R. Fenichel, M.D., Ph.D., HFD-110, Deputy Division Director
Steven Mark Rodin, M.D., HFD-110, Medical Officer
Shari Targum, M.D., HFD-110, Medical Officer
James Hung, Ph.D., HFD-110, Statistician/Team Leader
John Lawrence, Ph.D., HFD-110, Statistician
Joseph Piechocki, Ph.D., HFD-810, Chemist (pre-meeting only)
Patrick Marroum, Ph.D., HFD-860, Clinical Pharmacology/Biopharmaceutics, Team Leader
Edward Fromm, HFD-110, Consumer Safety Officer

Cellegy Pharmaceuticals

Daniel Azarnoff, M.D., Senior Vice President, Clinical and Regulatory Affairs
Andrew Korey, Ph.D., Vice President of Clinical Affairs
J.C. Lee, Ph.D., Director of Development
John Dietrich, Ph.D., Vice President of Research and Development

Consultants



Background

Dr. Stephen Gorfine originally submitted nitroglycerin ointment for the treatment of anal fissures as an IND on June 1, 1994. Dr. Gorfine subsequently transferred ownership of IND 45,326 to Cellegy Pharmaceuticals on January 6, 1998.

The firm met with the Division on January 14 and February 24, 1998 to discuss phase 3 trial designs for nitroglycerin ointment in patients with chronic anal fissures. Unfortunately, the phase 3 clinical trial conducted by the firm to show efficacy in healing chronic anal fissures failed to show significance over placebo. The company has now requested a meeting with the Division to discuss the results of the trial and to obtain guidance on how to proceed with development of their product.

Meeting

The firm opened the meeting by stating that the placebo group in their efficacy trial for healing chronic anal fissures showed an inexplicably high improvement rate. The firm noted, however, that they measured a fixed amount of nitroglycerin ointment before applying whereas other studies that showed a benefit over placebo did not. The firm also thought that they might be able to show efficacy in healing if they better differentiated between patients with acute versus chronic anal fissures.

The firm mentioned that pain relief, although not a primary endpoint, was demonstrated with the 0.2% and 0.4% preparations (see appended slide). They noted that pain is a significant complaint of patients with anal fissures and the surgical procedure needed to fix these fissures is expensive. Dr. Fenichel stated that pain relief would have to be specified as a primary endpoint at the start of the trial for it to have validity. Dr. Lipicky added that the results of their trial showing nominal significance for pain relief, although promising, would need to be confirmed with another trial. Dr. Fenichel outlined two approaches the firm might take in deciding which endpoint to focus on:

1. Redesign the trial to better exclude acute anal fissure, and see if significance can be achieved with respect to healing.
2. Ignore healing altogether, and focus on pain relief. Another study similar in design to the one conducted would be acceptable.

The firm indicated that they favored a trial focusing on pain relief and asked if a trial using a fixed frequency (e.g., TID), placebo, 0.2% and 0.4% strengths of ointment would be acceptable. Dr. Lipicky stated that placebo and 0.4% are acceptable, although the Division usually prefers more than one dose level. The firm mentioned that the 0.4% strength had relatively few dropouts from headaches. Dr. Fenichel, noting the relatively few dropouts at the 0.4% strength and a dose-response curve showing a positive slope, suggested that the firm consider increasing the dose further. One way to do this would be to use several doses (e.g., 0.4%, 0.6%, 0.8%) for pain relief and to reduce the dose back to a lower strength only if encountering significant side effects (e.g., headaches). This approach would be more informative while preserving the intent-to-treat analysis. The firm said that (b) (4)

Measurement of Pain Relief

Dr. Lipicky asked the firm how pain was measured. The firm said they used a visual analogue scale to measure pain. Dr. Lipicky asked at what time of the day were pain measurements taken. The firm indicated that pain measurements were taken in the morning, afternoon, and at bedtime and that the three measurements were averaged for that day.

Handling of Dropouts

Dr. Rodin and Dr. Hung asked how dropouts were handled statistically in the trial. The firm mentioned that they were excluded at timepoints where the data were missing. They added that a primary analysis in a future trial would include a comparison of slopes.

NDA Submission

The firm asked the Division if there were any issues that might affect the submission of this application as a NDA. Dr. Lipicky stated that Dr. Piechocki, the review chemist for this product, wanted a separate CMC pre-NDA meeting when the firm was ready to submit a NDA. Dr. Piechocki's additional concerns are as follows:

1. Specifications were too wide, they need to be narrowed down
2. Samples from the filled tubes of nitroglycerin weren't uniform in concentration.

The firm noted that the labeling of some nitroglycerin products were missing data relating to Carcinogenesis, Mutagenesis, and Impairment of Fertility. Dr. Lipicky indicated that he was unaware of this but said we would review the labeling of all nitroglycerin products. He added that the firm should submit pharmacology/toxicology data prior to submission to see if it would be supportive of approval of the NDA.

Dr. Lipicky suggested that the firm send in their proposed Statistical Plan for Analysis of the next trial for our review before proceeding with the trial.

Dr. Lipicky reminded the firm that if they were using information that was not their own (excluding the U.S. Army Pharm./Tox. Study), they would have to document how they were not infringing the patent rights of others.

Priority Review

The firm asked if the Division would consider a priority NDA review for nitroglycerin ointment in treating pain in patients with chronic anal fissures. Dr. Lipicky said he was uncertain because there was an absence of data documenting morbidity or mortality with pain relief.

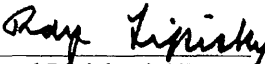
Conclusion

The firm plans on conducting a confirmatory trial showing pain relief in patients with chronic anal fissures. Dr. Lipicky has asked the firm to submit the Statistical Plan of Analysis of their next trial and any pharm/tox data that would be used for a future NDA submission. The Division will review the labeling of all nitroglycerin products to see if there are any deficiencies with respect to Carcinogenesis, Mutagenesis, and Impairment of Fertility.

Minutes Preparation:


Edward Fromm

Concurrence Chair:


Raymond Lipicky, M.D.

ef/12-9-99/12-20-99

Rd: JPiechocki/12-13-99
PMarrouom/12-14-99
JLawrence/12-14-99
JHung/12-15-99
STargum/12-15-99
SRodin/12-16-99
RFenichel/12-16-99

cc: IND 45,326
HFD-110
HFD-110/Blount
HFD-110/EFromm/SMatthews

Table 1

Percent Pain Decrease from Baseline
Significance Levels Based on Mixed-Model
Applied to Raw Data for Intent to Treat Sample

Day	All Subjects				Baseline AVG > 25			
	0.0	0.1	0.2	0.4	0.0	0.1	0.2	0.4
Average Pain								
7	25	42	42**	40**	32	37	52**	44*
14	42	46	46	49**	46	43	55*	58*
21	39	51*	51*	58***	47	55	60*	65**
28	52	58	58*	60***	55	53	65*	68**
35	50	57	57*	66***	57	59	66	75***
42	54	63	63	65***	56	60	70	71**
49	54	67	67**	69***	57	67	74*	78**
56	51	65	65**	72***	57	66	76**	80***
Defecation Pain								
7	42	41	43	51	38	37	49	53
14	55	43	44	59	46	40	44	60
21	53	56	47	64**	50	54	46	67
28	57	60	55	68**	46	58	58	68*
35	58	62	58	72***	52	58	62	77***
42	61	65	61	72**	53	62	66	72**
49	61	65	66	77***	52	64*	74**	81***
56	61	67	67	80***	55	65	78*	83**
Worst Pain								
7	39	39	46	48*	39	38	49	48
14	55	46	52	59*	49	47	53	59
21	56	60	56	65***	52	62	59	68*
28	61	61	61	71***	55	58	65	73**
35	62	66	61	74***	52	63	66	78**
42	64	66	67	74***	58	65	72*	74**
49	61	71	70*	77***	57	71	77**	79**
56	60	71	69	79***	57	70	79**	82**

* $p < .05$

** $p < .01$

*** $p < .001$

MAR 31 1998

MEETING MINUTES

Date: February 24, 1998

Subj: IND 45,326 Nitroglycerin Ointment for Rectal Fissures
Protocol DiscussionSponsor: Cellegy Pharmaceuticals, Inc.
Foster City, Ca, 94404

Meeting Chair: Raymond Lipicky, M.D.

Recorder: Gary Buehler

Sponsor Lead : Daniel Azarnoff, M.D.

Attending:

Cellegy

Daniel Azarnoff, M.D. VP, Clinical/Regulatory Affairs

(b) (4)

FDA

Raymond Lipicky, M.D.	Dir., Div. of Cardio-Renal Drug Prod., HFD-110
Charles Ganley, M.D.	Medical Group Leader, HFD-110
Steven Rodin, M.D.	Medical Reviewer, HFD-110
Kooros Mahjoob, Ph.D.	Biostatistics Reviewer, HFD-710
Emmanuel Fadiran, Ph.D.	Biopharmaceutics Reviewer, HFD-860
Gary Buehler	Project Manager, HFD-110

BACKGROUND

Cellegy recently acquired the rights to IND 45,326 from Dr. Stephen Gorfine. They met with the Division on January 14, 1998 to discuss the requirements for an application for nitroglycerin ointment for chronic rectal fissures. At that meeting, the firm discussed various development programs with the Division. They have now finalized a protocol and development plan that they would like to discuss with the Division.

DISCUSSION**Serum Nitroglycerin Sampling**

The firm has proposed doing a parallel-group, placebo-controlled study using 3 concentrations (0.1, 0.2, and 0.4%) and two dosage regimens (BID and TID) plus placebo groups for each regimen. When they proposed this design at the January 14 meeting, they proposed to sample blood levels of nitroglycerin in a subpopulation at 5, 10, 30, 60 and 120 minutes after application of the first dose on days 1, 14, 28 and 42. This proposal was not included in their present protocol.

Dr. Lipicky said that these blood levels would be useful if there was something of concern related to blood levels of nitroglycerin (patients with angina, tolerance concern). He said that it would be reasonable to document the blood levels. The sampling need not be extensive, and it

could be done in a separate study if preferred.

Statistical Plan

The primary endpoint for the study is fissure healing. For a given subject, the study will continue until the fissure heals or 56 days of treatment have passed. The proposed primary statistical analysis is a survival analysis, using the time-to-event (Healing). The firm plans to model the effects of dosage (0, 0.1, 0.2, and 0.4% nitroglycerin) and frequency (BID and TID) on time to fissure healing using a proportional hazards Cox regression.

Rather than having a series of six comparisons to placebo, some of which may be significant and some of which may not, it would be preferred that there be one way that nitroglycerin is compared to placebo. Once the main test of efficacy is made (NTG vs. placebo), all other comparisons will be descriptive and will be used to create instructions for use. A choice must also be made prospectively as to how the primary analysis will be done (survival analysis or intent-to-treat patient groups). We will expect that both analyses be made, but one must be prospectively declared as primary.

Assessment of Pain Relief

It was suggested that a double dummy technique be employed to give the BID patients a third daily dose. This would make the comparison between the BID and TID doses more valid. While it was recognized that this would be of benefit, it was difficult to determine how it could practically be done.

Sitz Baths

The firm was asked about prohibiting sitz baths during the trial. It was recommended that the usual standard of care should not be interrupted during the trial. Dr. Azarnoff said that this was a recommendation of Dr. Gorfine. He thought it could be deleted.

Unit Dosing

The firm was asked how they were going to assure that the dosing of the product was accurate and consistent. It was recommended that they unit-dose their product. The firm stated that (b) (4)

[REDACTED]

Other Issues

It was confirmed that the firm was using a standard, validated metric for pain relief.

It was emphasized that the observer that judges healing should not have any access to the case report form, nor should they know if the patient has developed a headache.

It was suggested that a 4 week follow-up may not be long enough to look for recurrence.

The firm was informed that they could exclude pregnant women from their trial.

The firm was informed that they could treat patients open-label with nitroglycerin ointment after the 56 day trial period is over, but they must report the results of the treatment.

Minutes Taken by: Gary Buehler 3/31/98

Gary Buehler

Concurrence, Chair Ray Lipicky

Raymond Lipicky, M.D

Orig IND

HFD-110

HFD-110 GBuehler

HFD-110 SBenton

RD:	SRodin	3/30/98
	CGanley	3/31/98
	KMahjooob	3/31/98
	EFadiran	3/31/98

DP 115 4 1998

MEETING MINUTES

FEB 2 1998

Date: January 14, 1998

Subj: IND 45,326 Nitroglycerin (b)(4) % Ointment for Rectal Fissures
Clinical Development Meeting

Sponsor: Cellegy Pharmaceuticals, Inc.

Meeting Chair: Raymond Lipicky, M.D.

Recorder: Gary Buehler

Sponsor Lead: Daniel Azarnoff, M.D.
Stephen Gorfine, M.D.

Attending:

Cellegy

Daniel Azarnoff, M.D. VP, Clinical and Regulatory Affairs

Michael Francoeur, Ph.D. VP, Research and Development

(b)(4)

FDA

Raymond Lipicky, M.D. Dir., Div. of Cardio-Renal Drug Prod., HFD-110

Charles Ganley, M.D. Medical Team Leader, HFD-110

Steven Rodin, M.D. Medical Reviewer, HFD-110

Kooros Mahjoob, Ph.D. Statistical Reviewer, HFD-710

Emmanuel Fadiran, Ph.D. Biopharm Reviewer, HFD-860

Gary Buehler Project Manager, HFD-110

BACKGROUND

Dr. Stephen Gorfine submitted an individual investigator IND for nitroglycerin ointment (originally (b)(4)%, now 0.2%) on May 20, 1994. After some dialog with Mr. Buehler, it became apparent that Dr. Gorfine intended to develop this product commercially for the treatment for rectal fissures. After unsuccessfully working with some consultants, Dr. Gorfine transferred sponsorship of the IND to Cellegy Pharmaceuticals, Inc. This meeting was requested to discuss the requirements for approval of nitroglycerin ointment 0.2% for rectal fissures.

AGENDA

The firm submitted the following questions:

1. Are the data provided in the pre-meeting submission sufficient to support filing of the NDA?
2. If not sufficient, specifically, what data would be required to support such a filing?

DECISIONS

1. The data submitted in the pre-meeting package are not sufficient to support an NDA filing. There is an inadequate number of patients, an inadequate exploration of the effective

concentration and interval and no way to assess if tolerance develops. One also does not know if the problem will recur after discontinuation of treatment.

The applicant was informed that normally 5 to 10 published papers equals one good clinical trial. The firm was also informed that they have no data linking the product(s) used in the published trials with the product that they intend to market.

2. The firm proposed the following programs:

(b) (4)

The above program could result in an approval if two trials of the above design were completed successfully. Having less than 2 trials would make the approval of the application very questionable. It would also be uncertain what the labeling would say with such a sparse data base.

(b) (4)

This program would be acceptable with a convincing p value (since there is only one trial). A mechanism to evaluate if tolerance develops should also be included. The firm stated that they thought that they could get the right to reference for the Kennedy and Lund trials.

ADDITIONAL ISSUES

1. Evaluation of tolerance can be done in a randomized subset of the clinical trial. This evaluation can be made by doing a 2 week (or shorter) discontinuation arm.
2. The number of applications used in the clinical trial (QD, BID, QID) would be up to the applicant.
3. The primary efficacy variable(s) must be chosen prospectively. They can be any one of the doses and intervals chosen. If multiple doses are chosen as primary endpoints, the alpha must be allocated accordingly. Dose response could also be chosen as the primary endpoint by looking for a non-zero slope for dose response.
4. Pain relief should be evaluated at least at every office visit. A one-tailed statistical analysis for this evaluation would not be acceptable.
5. The firm asked if their manufacturing and controls plan would be acceptable (see separate sheets). No one from chemistry was present at the meeting, but Mr. Buehler said that he would ask Dr. Short to review their proposals.

Addendum

Dr. Short said that their proposal was acceptable except for using smaller scale equipment for the registration batches instead of using the commercial scale equipment (and just making less

product). Ideally, he said they should use the same equipment that will be used for the commercial batches. He conceded, however, that sometimes this is not possible.

SUMMARY

The firm was told that they should prepare their final protocols and meet again with the Division to discuss their acceptability.

Minutes taken by: Gary Buehler 2/2/98

Gary Buehler

Concurrence, Chair Ray Lipicky

Raymond Lipicky, M.D.

Orig IND

HFD-110

HFD-110 GBuehler

HFD-110 SBenton

RD:	SRodin	2/2/98
	CGanley	1/29/98
	KMahjob	2/2/98
	EFadarin	2/2/98
	JShort	2/2/98

4 Pages have been Withheld as b4 (CCI/TS) immediately following this page

OCT 3 1996

MEETING MINUTES

Date: September 25, 1996 10:30 AM CR "F" WOC II

Subj: IND 45,326 Nitroglycerin Low Concentration Oint

Sponsor: Neptune Pharmaceutical Corporation
 Stephen R. Gorfine, M.D.
 25 East 69th Street
 New York, NY 10021

Recorder: Gary Buehler

Chair: Raymond Lipicky, M.D. Ext. Const. Chair: Stephen Gorfine, M.D.

FDA Attendees:

Raymond Lipicky, M.D.	Dir., Div. of Cardio-Renal Drug Products, HFD-110
N. Stockbridge, M.D., Ph.D.	Supervisory Medical Officer, HFD-110
Steven Caras, M.D., Ph.D.	Medical Reviewer, HFD-110
Kooros Mahjoob, Ph.D.	Statistical Reviewer, Div. of Biometrics, HFD-710
Gary Buehler	Regulatory Health Project Manager, HFD-111

Neptune Attendees

Stephen Gorfine, M.D.	President

(b) (4)

BACKGROUND

Dr. Gorfine submitted his individual investigator IND for Nitroglycerin Ointment 0.5% on May 20, 1994. Dialog between Dr. Gorfine and Mr. Buehler developed, and it then became apparent that Dr. Gorfine intended to develop this therapy commercially. Dr. Gorfine was advised to hire some consultants to assist him with the very large task of developing a therapy for commercial marketing. Dr. Gorfine initially hired (b) (4) as consultants. They helped him do an initial study that was not successful using pain as an endpoint. He attributed the failure to the trial design suggested by the consultants. He recently hired (b) (4). He and his consultants have requested to discuss his proposed clinical program with the Agency.

DISCUSSION POINTS/DECISIONS**Manufacturing and Controls**

It was confirmed that Dr. Gorfine has contracted with a pharmaceutical manufacturer to make his nitroglycerin ointment. He stated that the manufacturer has an ANDA to manufacture the commercially available nitroglycerin ointment (2%). It was also confirmed, however, that the information relating to the manufacture of the IND product has not been submitted to the IND. Dr. Lipicky said that information relating to the method of manufacture, the source of the ingredients and packaging materials, and the final testing and stability of the product must be submitted to the IND. This can be done directly or via DMF reference. Since the manufacturer has an approved ANDA, Dr. Lipicky said that they would know what would be required.

Animal Studies

It was confirmed that animal studies would not be required for the application. The standard skin irritation studies done routinely for an external preparation can be completed in man (in the hemorrhoid trial).

Clinical Development Program - Anal Fissures

Two trials, each statistically significant with a p value of 0.05, will be required for approval of the therapy. A dose response trial is planned for the anal fissure program. A safety data base would also have to be submitted. The numbers required would depend on the effect; clinical experience could be used, but all adverse events from open label trials would be blamed on the drug. Dr. Lipicky estimated that from 500 to 1000 patients (total-both indications) in controlled trials would be required. Dr. Gorfine was also advised not to exclude cardiac patients.

Endpoints

The endpoints chosen for the anal fissure trial were pain relief and healing. It was noted that healing is quite subjective. It was therefore recommended that each center have one person designated to evaluate the healing of the fissures. This person should be blinded to the patient's history and should not be involved in their day-to-day care. Dr. Lipicky said that an atmosphere must be created where a non-biased decision can be made.

In addition, the firm plans to use pain as an endpoint. It was explained that if pain and healing were used as independent primary endpoints, a p value of 0.025 would have to be achieved for each endpoint. If, however, one were chosen as the primary endpoint and the other a secondary endpoint, a p value of 0.05 would be required for the primary endpoint. If both endpoints are significant in this design, the secondary endpoint could be claimed as an indication. If, however, the secondary endpoint is significant, but the primary is not, the trial will fail.

Dose

The proposed doses for study in the anal fissure study are 0.05, 0.1, 0.2, and 0.3%. Dr. Lipicky said that he would like to see a wider range of doses studied and suggested going to 1%. Because the vascular effects of nitroglycerin exhibit tolerance, he also recommended studying different dosing regimens, specifically one that would incorporate a dose-free interval of at least 12 hours to determine whether the tolerance to the vascular effects would affect healing. Dr. Lipicky said that one or two arms could be designated to deny the null hypothesis. These would be the doses thought most likely to be effective. The other arms (higher dose, dosing regimen with 12 hour dose-free interval) could be smaller.

The concept of optimal randomization was also suggested. This method is used in smaller trials to assure that randomization with respect to various cofactors is achieved.

Clinical Development Program - (b) (4)



Blood Levels

Dr. Lipicky stated that blood levels of nitroglycerin need not be measured in any of their trials.

ACTION ITEMS



Minutes prepared by: *Gary Buehler*

Gary Buehler

Concurrence, Chair *Ray Lipicky*

Raymond Lipicky, M.D.

Orig IND

HFD-110

HFD-110 GBuehler

HFD-110 SBenton

RD: SCaras 10/2/96, NStockbridge 10/2/96, KMahjoob 10/2/96