

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-359

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 021359	NDA Supplement #: N/A	Efficacy Supplement Type SE-
Proprietary Name: Rectiv Established/Proper Name: nitroglycerin Dosage Form: ointment Strengths: 0.4%		
Applicant: ProStrakan, Inc.		
Date of Receipt: July 1, 2004 April 15, 2004 September 30, 2009 December 21, 2010		
PDUFA Goal Date: Not Approvable December 23, 2004 Approvable July 7, 2006 Complete Response March 30, 2010 June 21, 2011		Action Goal Date (if different): N/A
Proposed Indication(s): relief of pain of moderate to severe chronic anal fissure		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA: 20145 Nitro-Dur	Genetic toxicology; reproductive and developmental toxicology; mechanism of action
Published Literature	Nonclinical pharmacology

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The Applicant bridged the proposed product to the referenced product via literature support. A BA/BE study was not conducted, however the Applicant submitted information collected from the literature that demonstrated that nitroglycerin AUC and Cmax values from nitroglycerin ointment 0.4% were similar or less to Nitro-Dur® 40 cm² (0.8 mg NTG/hr) patch. It is noted that the submitted data had several underlying assumptions and extrapolations that were deemed acceptable by the reviewing Clinical Pharmacologist.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

If "NO," proceed to question #5.

*If "YES", list the listed drug(s) identified by name and answer question #4(c).
Nitro-Dur*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Nitro-Dur	NDA 020145	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new indication, treatment of chronic anal fissure, a new formulation, (0.4% ointment), and new route of administration, (intra-anal).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES ☐ NO ☒

If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES ☒ NO ☐

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): approved generics are listed in the Orange Book

Nitromist (Novdel), Nitroglycerin in Dextrose (Baxter), Nitroglycerin (Hospira), Nitrolingual Pump Spray (Pohl Boskamp), and Nitrostat (Pfizer)

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 5,504,117 and 5,693,676

No patents listed ☐ proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- ☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- ☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- ☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): 5,504,117 and 5,693,676

- ☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- ☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- ☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the

NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 5,504,117 and 5,693,676

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): September 16, 2004 to Key Pharmaceuticals

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES ☐ NO ☒ Patent owner(s) consent(s) to an immediate effective date of approval ☒

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

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: June 17, 2011

To: Chris Hilfiger – Regulatory Project Manager
Division of Anesthesia, and Analgesia Products (DAAP)

From: Mathilda Fienkeng – Regulatory Review Officer
Sheneé Toombs – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: DDMAC draft labeling comments
NDA 021359 RECTIV (nitroglycerin) Ointment 0.4%

DDMAC has reviewed the proposed product labeling (PI) and the Patient Package Insert (PPI), for RECTIV (nitroglycerin) Ointment 0.4%, submitted for DDMAC review on June 15, 2011. The following comments are provided using the substantially complete version of the labeling sent via email on June 15, 2011, by Chris Hilfiger

DDMAC's comments are provided directly in the attached marked-up copy of the PI and PPI. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

13 Pages of Draft Labeling have been Withheld as b4 (CCI/TS) immediately following this page

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

/s/

MATHILDA K FIENKENG
06/17/2011

LATOYA S TOOMBS
06/17/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: May 12, 2011
Application Type/Number: NDA 021359
To: Robert Rappaport, MD, Director
Division of Anesthesia and Analgesia Products
Through: Zachary Oleszczuk, Pharm.D., Team Leader
Kellie Taylor, Pharm.D., MPH, Associate Director
Todd Bridges, R.Ph., Acting Deputy Director
Division of Medication Error Prevention and Analysis
From: Manizheh Siahpoushan, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis
Subject: Label and Labeling Review
Drug Name(s): Nitroglycerin Ointment, 0.4%
Applicant/sponsor: ProStrakan, Inc
OSE RCM #: 2011-1087, 2011-1140

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1 INTRODUCTION

This review evaluates the container label, carton and insert labeling for Nitroglycerin Ointment 0.4% for any potential to contribute to medication errors. This review is in response to the March 22, 2011 submission from ProStrakan, Inc. Additionally, Division of Anesthesia and Analgesia (DAAP) specifically asked DMEPA to consider the use of a Medication Guide for this production.

Revisions are necessary to the packaging to include a dosing device or single dose packets to ensure appropriate administration. Additionally, from a medication error perspective, the use of a Medication Guide does not seem warranted because it is unclear that there are medication error risks that require mitigation.

The review of the Proposed Proprietary Name (b) (4) is currently pending with DMEPA under another cover.

1.1 REGULATORY HISTORY

Cellegy Pharmaceuticals, Inc. submitted the proposed proprietary name, Cellegesic (Nitroglycerin) Ointment, USP, 0.4% (NDA 021359) on June 30, 2004. DMEPA reviewed and had no objection to the proposed proprietary name, Cellegesic (OSE Review # 01-0097-2 dated August 25, 2004). DMEPA also included recommendations on container label, carton, and insert labeling in this review. The application received a non-approvable letter on December 23, 2004. In the fourth quarter of 2006, Cellegy Pharmaceuticals sold the NDA including the US rights for Cellegesic to ProStrakan, Inc. ProStrakan resubmitted the NDA on September 30, 2009. DMEPA found Cellegesic unacceptable in OSE Review # 2009-1999 dated December 29, 2009 because of orthographic and phonetic similarities between Cellegesic and the already marketed products, Calagesic and Alagesic. The name was withdrawn and the name Rectogesic was submitted for review on January 14, 2010. DMEPA found the name Rectogesic unacceptable in OSE Review # 2010-278, dated April 15, 2010, due to vulnerability to name confusion with the already marketed Rectagene, Relagesic, and Rectacaine. The Applicant withdrew the name Rectogesic on March 22, 2011 and submitted the name (b) (4) for primary consideration and (b) (4) for alternate consideration.

2 METHODS

Since Nitroglycerin Ointment 2% (Nitro-BID) has been marketed since May 28, 1981, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database to identify any medication errors involving Nitroglycerin Ointment label and labeling. These errors may be indicative of errors that can occur with the proposed product.

Additionally, DMEPA evaluated the proposed container label, carton, and insert labeling using Failure Mode and Effects Analysis¹ (FMEA), principles of human factors, and lessons learned from the post marketing experience to identify areas that can contribute to medication errors.

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) SELECTION OF CASES

Search of the FDA Adverse Event Reporting System (AERS) database was conducted on April 5, 2011 using the following criteria: Active Ingredient "Nitroglycerin", Trade Name "Nitro-BID", verbatim terms "Nitrob%" and "Nitrogly%", MedDRA reaction terms "Medication Errors" (HGLT), "Product Label Issues" (HLT), "Product Quality Issue" (PT), and date limit of

¹ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

May 28, 1981 (date of approval of Nitroglycerin Ointment 2%) to April 5, 2011. Also, because there are multiple formulations and routes of administration of Nitroglycerin available in the market, the search was further limited to “topical” and “unknown” Route of Administration. We did not include the rectal route of administration since none of the Nitroglycerin products are approved for rectal administration. Duplicate reports were combined into cases. Those cases not pertaining to errors due to concomitantly administered drugs were excluded from further analysis. All cases of medication error were evaluated and grouped by the type of error. Each case was evaluated for the root cause. Additionally, cases that described errors related to Nitroglycerin patches or sprays were also eliminated.

2.2 LABELS AND LABELING

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the proposed container label, carton, and insert labeling submitted on March 22, 2011 by the Applicant (see Appendix A).

3 RESULTS AND DISCUSSIONS

The following sections describe the results of DMEPA’s medication error searches and labels and labeling evaluation.

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH RESULTS

The AERS search identified 22 (n=22) reports. After eliminating cases as described in section 2, three cases remained. One case (ISR #1549865) described accidental exposure to Nitroglycerin ointment by a nurse who thought she was using another unspecified ointment, and resulted in headache. The second case (ISR #4525572) describes a medication error in the pharmacy where a prescription for Nitroglycerin 0.2% ointment to be compounded, was entered and filled as Nitroglycerin ointment 2% commercial product. The cause of error was determined to be “short staffed and very busy after a holiday”. The last case (ISR #5930679) relevant to this review describes a reporter expressing concern about the measuring guide provided with the Nitroglycerin 2% Foilpacs. The reporter states that the paper applicators supplied with the Foilpacs measure the dose up to 2 inches. The applicator displays a width which is supposed to represent the width of the tape of ointment dispensed from the Foilpac. According to the reporter, the tape is much thinner in width than that represented by the paper applicator and can supply about 4 inches of Nitroglycerin ointment. Patients who are prescribed 1 inch of Nitroglycerin ointment are actually receiving about half of the amount they have been prescribed. For a complete list of ISR numbers for the AERS cases, refer to Appendix B.

3.2 LABEL AND LABELING RISK ASSESSMENT

Our evaluation of the proposed container label, carton, and package insert labeling noted areas of improvement. The following deficiencies were identified:

- Inappropriate presentation of the established name, dosage form and strength on container label and carton labeling
- The company name and logo competes for prominence with other important information such as the proprietary name, established name and strength
- The inactive ingredients do not appear on the container label and carton labeling
- Lack of prominence of the route of administration on the container label and carton labeling
- Inconsistent use of reference to the route of administration on container label, carton, and insert labeling

- Presence of trailing zeros on container label, carton, and insert labeling
- The dosage guideline only appears on the carton labeling

Additionally, because it is not clear if DMEPA's Label and labeling comments in OSE Review # 01-0097-2 dated August 25, 2004 were communicated to the Applicant, we have incorporated any comments that are still relevant to this review.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the proposed container label, carton, and package insert labeling identified areas of improvement to minimize medication errors. Section 4.1 *Comments to the Division*, contains our recommendation for the insert labeling and section 4.2 *Comments to the Applicant*, contains our recommendation for the proposed container labels and carton labeling for (b) (4).

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have any further questions or need clarifications on this review, please contact Azeem D Chaudhry, OSE Project Manager, at 301-796-3813.

4.1 COMMENTS TO THE DIVISION

We have the following recommendations for the insert labeling:

A. Medication Guide

Since there does not appear to be a specific medication error risk that is attempting to be mitigated by the use of a Medication Guide, we do not think that the use of a medication guide is needed at this point. Appropriate administration directions for patient and healthcare providers are available in the prescribing information and the Patient Information leaflet.

B. Prescribing Information

1. We recommend creating a separate measuring device (Dosage Guide) such as a reusable applicator or a pad of disposable measuring devices seen with other nitroglycerin ointments other than that presented on the carton labeling, and include with the tube (i.e. rubber-banded to the tube) inside the carton. As it currently appears on the carton, the Dosage Guide can easily be covered by pharmacy labels affixed to the carton labeling, if the pharmacist or the technician is not familiar with the product. Additionally, the carton can be discarded by patients if they have not been advised about the Dosage Guide on the carton labeling. If a separate measuring device is created, include a warning statement on the principal display panel to warn patients that the measuring device is included inside the carton. The statement can appear as follows:

"Dosage Guide included inside the box"

2. If a separate measuring device is not created, include a warning statement on the principal display panel to warn the patients to keep the box for the Dosage Guide. The statement can appear as follows:

"Do not discard the carton- Dosage Guide included on two sides of the carton"

3. As an alternative to a measuring device, we recommend developing single dose foil packs so that a measuring device would not be needed.

4. Revise the presentation of the proprietary name, established name, dosage form and strength throughout the package insert and patient Information to appear as follows: Brandname (Nitroglycerin) Ointment 0.4%.
5. Remove the trailing zeros from "1.0 inch" where it appears throughout the package insert and the Patient Information. The use of trailing zeros is error-prone and can result in ten-fold dosing error if the decimal is not seen (i.e. '1.0' is misinterpreted as '10'). In June 2006, FDA launched a campaign in conjunction with ISMP to prevent the use of error-prone dose designations such as trailing zeros in prescribing. As part of this campaign, FDA agreed not to approve error-prone dose designations in labeling because they are carried on to the prescribing practice.
6. Revise the Dosage and Administration Section in the Highlights and the Full Prescribing Information to include the amount of ointment that should be applied (1 inch). This will make it easier for healthcare professionals to know the exact amount that needs to be applied by patients. The new statement should appear as follows:

Apply 1 inch of ointment (375 mg of ointment equivalent to 1.5 mg
Of Nitroglycerin) intra-anally every 12 hours for up to 3 weeks
7. Ensure the consistency of the route of administration statements on container label and carton labeling as well as in the package insert labeling and Patient Information. The insert labeling states "For intra-anal use" while the container label, carton labeling, and the Patient Information state (b) (4). The tration should be presented as either (b) (4) or "For Intra-anal Use Only" throughout all the labels and labeling. We differ to the Division for the appropriate route that is correct by CDER standards.
8. Under Patient Counseling Information in the package insert, as well as under "Do not use Brandname if you:" in the Patient Information (second bullet point) de names of sildenafil, tadalafil, and vardenafil to appear as: Viagra (sildenafil), Cialis (tadalafil), or Levitra (vardenafil). Most patients may not be familiar with names of these products.

4.2 COMMENTS TO THE APPLICANT

A. All Container Label and Carton Labeling

1. Revise the presentation of the proprietary name, established name, dosage form and strength throughout the package insert and patient Information to be consistent with other topical products. The presentation should be as follows:

Brandname
(Nitroglycerin) Ointment 0.4%
2. Ensure the size of the established name is at least half as large as the letters comprising the proprietary name and has a prominence consistent with the proprietary name (type, size, color, font) in accordance with 21 CFR 201.10 (g)(2).
3. Include a qualitative list of active and inactive ingredients on the tube label where space allows as well as the carton labeling (can be included on the side panel). This is in accordance with 21 CFR 201.100 (b).

4. Include a usual dosage statement on the tube label where space allows as well as the carton labeling (can be included on the side panel). This is in accordance with 21CFR 201.100(b)(2). The statement can appear as follows:

Usual Dose: Apply 1 inch ointment rectally approximately every 12 hours.
Treatment should continue for up to three weeks or as instructed by your physician

Or

Usual Dose: See package Insert

5. Remove the trailing zeros from "1.0 inch". The use of trailing zeros is error-prone and can result in ten-fold dosing error if the decimal is not seen (i.e. '1.0' is misinterpreted as '10'). In June 2006, FDA launched a campaign in conjunction with ISMP to prevent the use of error-prone dose designations such as trailing zeros in prescribing. As part of this campaign, FDA agreed not to approve error-prone dose designations in labeling because they are carried on to the prescribing practice.
6. Delete the statement (b) (4) This statement will be duplicative after including the usual dosage statement.

B. Container Label

1. Relocate the company name and logo to the bottom portion of the label. As it is currently presented, the company name competes with the name of the product and can be distracting. Additionally, reduce the font size of the company name and logo.
2. Delete the quantity "30 g" directly under the established name. This information is presented in another location on the label and is duplicative. This will also create more space for information such as the usual dosage statement.
3. Relocate the route of administration (b) (4) or "For Intra-anal Use Only" to appear as the first statement below the established name.

C. Carton Labeling

1. Delete the blue/green graphic to create more white space and more prominence for important warning statements.
2. Relocate the company name and logo away from the product name. As currently presented, the company name is too close to the product name and can be distracting.
3. Relocate the route of administration (b) (4) or "For Intra-anal Use Only" to the space provided under the established name, after relocating the company name and logo. Additionally increase the prominence of the statement by bolding it.
4. Relocate the warning statement "Use within 8 weeks of first opening" to the principal display panel in the white space provided, after deleting the blue/green graphic.

5 REFERENCES

1. *Adverse Events Reporting System (AERS)*

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. *Previous OSE Reviews*

Roselle, Nora. OSE Review # 01-0097-2, Proprietary Name Review

Jones Smith, Tselaine. OSE Review # 2009-1999, Proprietary Name Review

Jones Smith, Tselaine. OSE Review # 2010-278, Proprietary Name Review

Appendix A: (b) (4) Container Label and Carton Labeling Submitted to the FDA on March 22, 2011

Container (Tube) Label

Brandname
0.4% Ointment
(nitroglycerin)

 ProStrakan



30 g

(01)103 42747 235305

Each 375 mg dose of ointment (1.0 inch) contains 1.5 mg of nitroglycerin.

Keep out of the reach of children.

For Rectal Use Only. Read Patient Information before use.

Apply as instructed by your doctor.

Store at 20°-25°C (68°-77°F); excursions permitted between 15°-30°C (59°-86°F).
[see USP Controlled Room Temperature].

Keep the tube tightly closed. Use within 8 weeks of first opening.

Rx Only

30 g

Mfd. by: PHARBIL Waltrop GmbH, Im Wirtgen 25, 45731 Waltrop, Germany

Mfd. for: ProStrakan, Inc., Bedminster, NJ 07921

Lot/EXP:

xxxxxx x mm/yyyy



PH1138

Mfd. by: PHARBI, Waltrip GmbH,
Im Wirtgen 25,
45731 Waltrip,
Germany
Mfd. for: ProStrakan, Inc.,
Bedminster, NJ 07921

Rx Only



(01)103 42747 235305

Dosage Guide
1.0 inch

Each 375 mg dose of ointment (1.0 inch)
contains 1.5 mg of nitroglycerin.

For Rectal Use Only. Read Patient Information
before use.

Keep out of the reach of children.

Apply as instructed by your doctor.

Store at 20°-25°C (68°-77°F); excursions permitted
between 15°-30°C (59°-85°F). [see USP Controlled Room Temperature].

Keep the tube tightly closed.
Use within 8 weeks of first opening.

Rx Only

30 g

For more information call 1-800-XXXXXXX
or visit www.XXXXXXX.com.

Dosage Guide
1.0 inch

Brandname
0.4% Ointment
(nitroglycerin)
ProStrakan

Brandname
0.4% Ointment
(nitroglycerin)
ProStrakan

For Rectal Use Only

30 g

30 g

For Rectal Use Only

Brandname
0.4% Ointment
(nitroglycerin)
30 g
ProStrakan

ProStrakan

Appendix B: ISR Listings from AERS database

381216	4743585
631218	4882637
721482	5363333
1476817	5930679
1476825	6625920
1476831	6625892
1476840	7225134
1549865	7092280
1549888	7184987
4485419	7164423
4525572	7231371

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/s/

MANIZHEH SIAHPOUSHAN
05/12/2011

ZACHARY A OLESZCZUK
05/12/2011

KELLIE A TAYLOR
05/12/2011

ZACHARY A OLESZCZUK on behalf of TODD D BRIDGES
05/13/2011

RHPM Overview of NDA 21-359
Cellegesic (nitroglycerin) 0.4% Ointment
July 27, 2006

Sponsor: Cellegy Pharmaceuticals, Inc.
Type: 505(b)(2)/3P
Receipt Date: July 1, 2004
Class I Resubmission: April 15, 2005
User Fee Goal Date: June 15, 2005

Letter Issued: Approvable; July 7, 2005
Final Draft Labeling: N/A

Background

Cellegy Pharmaceuticals, Inc. (Cellegy) submitted a new 505(b)2 NDA (NDA 21-359) on June 22, 2001, received June 26, 2001, for Anogesic® (nitroglycerin) 0.2 and 0.4% Ointment intended for use as 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 fissure; they withdrew the NDA on April 25, 2002. Cellegy requested a Special Protocol Assessment on September 16, 2002 and we provided our response on November 1, 2002. Cellegy resubmitted the NDA for Cellegesic™ (nitroglycerin) 0.4% Ointment on June 30, 2004, received July 1, 2004, for the relief of pain associated with chronic anal fissure; the Division issued a not approvable letter on December 23, 2004. In a Type A meeting between Cellegy and the Agency on March 28, 2005, the Agency agreed to review (1) a re-analysis of the available data for all subjects with no imputation, censoring at the last observation, (2) an analysis of the effects of open-label use of mild analgesics on anal pain, and (3) an analysis of treatment effect by baseline pain, using the full range of pain, not just a single value (> 50-mm). Cellegy's submission of April 15, 2005 constituted a complete response to our not approvable letter dated December 23, 2004; the User Fee goal date for this Class I resubmission is June 15, 2005. The User Fee was paid with the initial NDA submission in June 2001 (ID # 4141). Cellegy requested, and the Division granted a deferral for pediatric studies until appropriate studies can be planned and completed in the pediatric population.

Cellegy Pharmaceuticals, Inc. listed NDA 20-145 Nitro-Dur, owned by Key Pharmaceuticals, Inc., as the reference drug, and they have provided patent certification and appropriate documentation showing that the NDA holder and patent owner received the notification as per 21 CFR 314.50(i)(1)(i)(A)(4); 314.52(b); and 314.52(e).

Medical Review

Class I Resubmission

In his review dated May 26, 2005, Dr. Marciniak stated that the NDA remains not approvable based on the following comments:

1. The first re-analysis of the primary endpoint for Study 3 is not new. This analysis was also done by the FDA statistical reviewer and presented in his primary review (December 17, 2004), and summarized in my primary review dated December 17, 2004. I still argue that by the appropriate, pre-specified analysis of this study, the study failed.
2. The analysis regarding analgesic use is interesting but not supportive by itself of approval. This analysis suggests that if there is a difference in pain, it is probably not related to analgesic use. The fundamental issue is that the data do not confirm conclusively that there is a difference in pain by treatment group.
3. The results by baseline pain quintile are not very convincing. If patients with more baseline pain respond better to treatment, why is the response in quintile 4 substantially better than in quintile

5? This analysis is merely hypotheses generating and would have to be confirmed conclusively with a new study.

Dr. Marciniak provided Medical comments regarding this Class I resubmission that are included in the approvable letter dated July 7, 2005.

Statistical Review

Dr. Hung's statistical comments regarding this Class I resubmission are included in the approvable letter dated July 7, 2005.

Labeling:

Labeling recommendations were not provided during this regulatory review cycle.

Advisory Committee Meeting

An Advisory Committee was held on April 25, 2006. The Advisory Committee voted 6 for approval and 6 for approvable.

Project Manager's Summary

An internal meeting was held on June 7, 2006. It was decided that an additional study would be needed for an approval. An approvable letter has been prepared for Dr. Temple signature. To my knowledge, there are no issues that might prevent taking regulatory action for this Class I NDA resubmission following an approvable letter.

John David, BSN, M.S. in HRM
Regulatory Health Project Manager

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/s/

John David
7/27/2006 08:02:29 AM
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RHPM Overview of NDA 21-359
Cellegesic (nitroglycerin) 0.4% Ointment
December 23, 2004

Sponsor: Cellegy Pharmaceuticals, Inc.
Type: 505(b)(2)/3P
Receipt Date: July 1, 2004
User Fee Goal Date: January 1, 2005
Letter Issued: Not Approvable; December 23, 2004
Final Draft Labeling: N/A

Background

Cellegy Pharmaceuticals, Inc. (Cellegy) submitted a new 505(b)2 NDA (NDA 21-359) on June 22, 2001, received June 26, 2001, for Anogesic® (nitroglycerin) 0.2 and 0.4% Ointment intended for use as 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 fissure. The trade name Anogesic was determined to be not acceptable to the Agency and the trade name Cellegesic™ was proposed and found to be acceptable. The NDA was withdrawn on April 25, 2002. Cellegy requested a Special Protocol Assessment on September 16, 2002 and we provided our response on November 1, 2002. Cellegy resubmitted the NDA for Cellegesic™ (nitroglycerin) 0.4% Ointment on June 30, 2004, received July 1, 2004, for the relief of pain associated with chronic anal fissure. This NDA is a resubmission of information included in the original NDA plus the data from an additional clinical trial. Cellegy has requested a deferral for pediatric studies until appropriate studies can be planned and completed in the pediatric population. The Division initially assigned a standard review to this NDA and subsequently reclassified the application as a priority review upon the sponsor's request. The User Fee was paid with the initial NDA submission in June 2001 (ID # 4141).

Cellegy Pharmaceuticals, Inc. has listed NDA 20-145 Nitro-Dur, owned by Key Pharmaceuticals, Inc., as the reference drug and they have provided patent certification and appropriate documentation showing that the NDA holder and patent owner received the notification as per 21 CFR 314.50(i)(1)(i)(A)(4); 314.52(b); and 314.52(e).

Division Director's Memorandums

In his Division Director's memo (#3) (follow-up on an email from the sponsor on December 22, 2004) dated December 23, 2004, Dr. Stockbridge stated that the sponsor's arguments do not alter his impression of these data. Whether there is a direct effect of treatment is not clear from study 03-02-01. Viewed most optimistically, the effect is, at best, a small fraction of the placebo effect. He remains of the opinion that these results make this application not approvable.

In his Division Director's memo (#2) dated December 20, 2004, Dr. Stockbridge stated that his comments are based on the reviews of Drs. Marciniak (clinical), Hung (statistics), Timmer (chemistry), Proakis (pharmacology) and Beasley (bipharmaeutics), and consideration for the sponsor's response (December 14, 2004) to the Division's discipline review letter dated December 10, 2004. He concluded that the appropriate regulatory action is not approval (NA). These data can not be made more compelling by further analysis and further study is unlikely to change one's impression of the overall magnitude of effect. If there is an effect of Cellegesic on anal pain, it is too small to be of clinical interest and comes with too high a cost—intolerable headache pain.

In his memo addendum (#1) (December 22, 2004) to a previous Divisional Memo (December 20, 2004), following up on a discussion of review issues with the sponsor (December 21, 2004), and a subsequent letter from the sponsor (December 21, 2004), Dr Stockbridge stated that the sponsor's arguments do alter his impression of these data. Whether there is a direct effect of treatment is not clear from study 03-02-01.

Viewed most optimistically, the effect is, at best, a small fraction of the placebo effect. He remains of the opinion that these results make this application not approvable.

Medical Reviews

Resubmission

In his review dated December 17, 2004, Dr Marciniak stated that from a clinical perspective he does not recommend approval of Cellegesic nitroglycerin (NTG) ointment for the relief of pain associated with chronic anal fissure. 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.

Financial disclosure is noted in Dr. Marciniak's medical review, page 16.

There are no labeling or postmarketing recommendations because the application is not recommend for approval.

Initial NDA

In the joint medical/statistical review dated February 27, 2002, Drs. Fredd and Hung state that Cellegy Pharmaceuticals submitted a NDA for nitroglycerin (NTG) ointment to relieve anal pain associated with anal fissures. Based on findings in the literature that NTG ointment relaxed the anal sphincter that could lead to anal fissure healing and relief of associated anal pain, the sponsor completed study NTG 98-02-01. The primary endpoint of that study was anal fissure healing. While that endpoint was NS, the secondary endpoint of relief of anal pain suggested a statistically significant effect in a linear mixed effects model for 0.4% BID NTG ointment compared to placebo. To prospectively test the pain relief hypothesis generated by that study, the sponsor performed study NTG 00-02-01. The primary hypothesis of efficacy was to be "tested via the treatment by week interaction (i.e., the rate of change in pain is different between active treated and vehicle treated subjects)." Using different parameters in a quadratic mixed effects model post-hoc, the sponsor found that NTG 0.4% BID average pain (primary endpoint) results were significantly different from placebo on linear trend and quadratic trend. The FDA statistician, Dr. Hung, using the linear model in the mixed effects model to evaluate the rate of change over time, as specified in the protocol and as used in the first study, found no significant difference for either active treatment group compared to placebo. Therefore using the mixed effects model with the methodology employed in the first study, the second study, the only confirmatory study provided, did not establish a significant difference between active drug and placebo.

PM Overview

Since the mixed effects model with the quadratic term gave somewhat different results, a hypothesis that the results differed over time was considered. To study this, Dr. Hung analyzed the rate of change in each weekly time period. For average pain, there seemed to be a difference in the rate of change for the 0.4% NTG group compared to placebo in the first week, but this was not sustained through the 56 days of treatment. At best there might have been a transient statistical difference, but even if this was the case, it would not translate into a meaningful clinical benefit for the patient since no benefit for NTG ointment could be found at the end of 56 days of therapy. In analyses of total pain relief or a difference in pain relief at the end of therapy, no differences comparing the active groups to placebo were found.

Importantly there were a large number of patients on active drug who developed headache. The headache was severe enough to lead to dropout in patients treated with NTG ointment, and those who remained in the study often required analgesic therapy. Headache should be considered a confounding element in the analysis of efficacy, since it led to more dropouts in the active treatment groups compared to placebo and might have influenced the anal pain results recorded by those patients who experienced headache on NTG ointment. Since no significant benefit on relief of anal pain was found in these clinical studies, and pain in the form of headache would be associated with NTG ointment treatment, a not approvable action is recommended.

Financial Disclosure is as noted in Dr. Fredd's memo dated April 2, 2002.

Pharmacology Review

In his review dated August 9, 2004, Dr. Proakis stated that Cellegesic™ Nitroglycerin Ointment 0.4% remains approvable from a non-clinical perspective. The non-clinical pharmacology and toxicological studies that were included in the June 2001 original submission were reviewed (Pharmacology/ Toxicology Review, 3/14/02). The resubmission of NDA 21-359 contains no new non-clinical pharmacology and toxicology studies requiring review. He recommends that the sponsor's draft labeling that refers to the results of animal toxicity studies be made consistent with labeling used for other nitroglycerin containing products. Labeling recommendations are noted in the Executive Summary on pages iv and v.

Biopharmaceutical Review

In her review dated October 25, 2004, Dr. Beasley states that on March 12, 2002, the Office of Clinical Pharmacology and Biopharmaceutics reviewed NDA 21-359, Anogesic, 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.

There are no new PK data contained in the current submission. The sponsor 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.

The labeling comments (page 9) for the Pharmacokinetics section of the biopharmaceutical review dated March 12, 2002 are still applicable to this submission.

Chemistry Review

In his review, dated December 13, 2004, Dr. Timmer stated that all CMC issues have been satisfactorily resolved at this time. The Office of Compliance has issued an ACCEPTABLE recommendation to all

manufacturing facilities. Labeling comments are noted on pages 19-22 of the CMC review dated December 7, 2004.

The sponsor requested and was granted a categorical exclusion to the Environmental Assessment as noted in his initial CMC review dated April 19, 2002.

Statistical Review

In his review dated December 17, 2004, Dr. Hung stated the previously submitted placebo-controlled clinical study NTG 00-02-01 seems to give a hint of a possible benefit of relief of pain associated with chronic anal fissure with nitroglycerin ointment 0.4% bid for a short term use. Study CP 125 03-02-01 was completed to confirm this hypothesis. Based on the reviewer's evaluation, this study fails to provide sufficient evidence in support of this hypothesis. The additional analyses for integrated summary of efficacy in the study report also add little to help conclude the claimed effect of pain relief.

DSI

In their memorandum dated December 21, 2004, Ms. Mease and Dr. Ball stated that the overall study data collected by Drs. Krivokapic and Stanojevic were collected in accordance with the protocol. However, the highly variable dose compliance introduces questions regarding the interpretation of the study results. The sponsor's identification that ointment could ooze from the ointment tube when the ointment tube was opened raised uncertainty about the interpretation of the dose compliance numbers.

In his memorandum dated March 19, 2002, Dr. El-Hage states that no major deficiencies were noted in the three sites inspected that could compromise the integrity of the data. Thus, the data reviewed are acceptable. No subsequent actions or follow up inspections should be undertaken.

Pediatric Rule

The Division granted (August 26, 2004) a deferral of pediatric studies in patients ages <1 month to 16 years for Cellegesic™ (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, requested that Cellegy Pharmaceuticals submit a general plan and timeline for their pediatric development program to the Division by December 27, 2004.

Labeling:

Labeling recommendations were not provided during this regulatory review cycle.

Advisory Committee Meeting

This application did not go before the Advisory Committee.

Project Manager's Summary

To my knowledge, there are no issues that might prevent taking regulatory action on this NDA.

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

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/s/

Daryl L. Allis
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MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH****CLINICAL INSPECTION SUMMARY**

DATE: December 17, 2004

TO: Daryl Allis, Regulatory Health Project Manager
Thomas Marciniak, M.D., Medical Reviewer
Division of Cardio-Renal Drug Products, HFD-110

THROUGH: Leslie K. Ball, MD, Chief, Good Clinical Practice Branch II
(HFD-47), Division of Scientific Investigations

FROM: Mary L. Mease, R.Ph., MPH, Reviewer, Good Clinical Practice
Branch II (HFD-47), Division of Scientific Investigations

SUBJECT: Evaluation of Foreign Inspections

NDA: 21-359

APPLICANT: Cellegy Pharmaceuticals, Inc.

DRUG: Cellegesic (nitroglycerin ointment)

PROTOCOL: CT 125-03-02-01

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Relief of pain associated with anal fissure

GOAL DATE TO PROVIDE
INSPECTION SUMMARY REPORT: December 1, 2004

PDUFA GOAL DATE: January 1, 2005 (HFD-110 wants to make a decision by
December 10, 2004)

I. BACKGROUND

Protocol CT 125-03-02-01 was an international, randomized, double-blind, placebo-controlled study. The primary endpoint was pain relief of anal fissures. A total of at least 150 subjects at about 40 clinical sites were to be enrolled in this study. Subjects applied 375mg of nitroglycerin ointment or placebo intra-anally twice daily for 56 days. Efficacy assessment was based on visual analog scores of pain and anal examination. A trained examiner blinded to all other aspects of the study performed anal examination. Post-treatment followup was performed by telephone every three months for a total of 12 months to determine if subjects received any additional treatment for their anal fissures.

The primary objective of this study was to determine the effect of nitroglycerin ointment versus placebo on the rate of change of the 24-hour average pain intensity associated with a chronic anal fissure over a 21-day treatment period. The secondary objective was to determine the effect of nitroglycerin ointment versus placebo on time to 50% improvement in the three-day average (i.e. a moving window) of 24-hour average pain intensity measurements associated with a chronic anal fissure. The study's tertiary objectives were to determine the tolerability of nitroglycerin ointment versus placebo and to determine the effect of nitroglycerin ointment versus placebo on

- the rate of change of the 24-hour average pain intensity associated with a chronic anal fissure over a 56-day treatment period,
- the rate of change of the pain intensity during the last bowel movement of the day any bowel movement occurs associated with a chronic anal fissure over a 21-day treatment period,
- the rate of change of the pain intensity during the last bowel movement of the day any bowel movement occurs associated with a chronic anal fissure over a 56-day treatment period, and

- complete healing of chronic anal fissures over a 56-day treatment period.

DSI met with DCRDP on 10/14/04 to discuss the site inspections. According to DCRDP, the two Yugoslavian sites, Drs. Krivokapic and Stanojevic, were selected because they had more favorable endpoint data than all other sites. DCRDP asked that, during the inspection, the FDA Investigator

- determine how the randomization was completed and documented and how the blind was maintained,
- determine what randomization procedure was used to enroll more than 8 subjects (these two sites enrolled 16 and 20 subjects), and
- thoroughly review drug disposition, including receipt from the sponsor, dispensing, and final disposition.

DCRDP posed the same three questions to the sponsor. As of 10/14/04, DCRDP had not received a response to the questions from the sponsor.

II. RESULTS (by site):

CI Name	City	Country	Inspection Date	Conducted under IND?	Classification
Zoran Krivokapic, MD	Belgrade	Yugoslavia	11/08-11/12/04	Yes	VAI
Goran Stanojevic, MD	Nis	Yugoslavia	11/15-11/18/04	Yes	VAI

1. Zoran Krivokapic, M.D. Koste Todorovica 6 11000 Belgrade Serbia and Montenegro, Yugoslavia

a. What was inspected

Records for all 20 subjects enrolled at this site were reviewed during the inspection. Comparison of diaries to CRFs did not reveal any discrepancies.

b. Limitations of inspection: None.

c. General observations/commentary

1. The dose compliance for 52 of 80 visits was <85% or >85%, the protocol-specified dose range. The dose compliance for four subjects (024-088, 024-292, 024-308, and 024-349) was greater than 115% (115.3%-295.4%) for all 4 visits (days 7, 21, 35, and 56). There were 3 subjects (024-303, 024-350, and 351) that had <85% compliance (47.6%-84.4%) for at least 3 of the 4 visits. There was documentation that the CI counseled subjects on compliance.
2. A 1 gram weight instead of a 200 gram weight was used to calibrate the scale used to weigh the study drug/placebo. This likely had a low impact on the study drug/placebo weights. The CI believed that the scale was properly calibrated at the start of the study.
3. Subject 024-292 had a number of adverse events including drowsiness, anal burning, itching of the face, vertigo, and flu-like syndrome. The CI attributed some of these adverse events to the study drug and the subject's dosing was interrupted several times before the subject was terminated from the study on day 44. Both the CI and subject believed she was receiving nitroglycerin ointment. However, she was assigned to placebo.
4. Subject 024-291 had two Sitz baths on days 22-29 and 32-34. This subject should have been withdrawn from the study since the protocol allows up to one Sitz bath per day. This subject was not withdrawn from the study. This subject received nitroglycerin ointment.

5. Subject 024-301 received placebo. Both the subject and CI believed the subject received nitroglycerin ointment (exhibit 7, p. 1).

Recommendation: Data from this site were collected in accordance with the protocol. However, the highly variable dose compliance introduces questions regarding the interpretation of the study results.

2. **Goran Stanojevic, M.D.**
Clinical Center of Nis Surgery clinic
Grace Taskovica 48
Nis, Yugoslavia

a. What was inspected

The records for all 16 subjects enrolled at this site were reviewed during the inspection. Comparison of diaries to CRFs did not reveal any discrepancies.

b. Limitations of inspection: None.

c. General observations/commentary

1. The dose compliance was above 115% (range: 141.5%-397.9%) for at least four subjects during one to three of the study intervals as follows (the subjects listed below may not be the only subjects that had dose compliance outside the protocol-specified range):

Subject No. Assignment		Approximate Compliance in % (Days 7, 21, 35, and 56)
095/M-N	active	332.3, 141.5, 170.0, 110.0
096/A-M	placebo	252.3, 90.86, 89.5, 116.2
297/D-D	placebo	306.6, 144.7, 107.6, 148.5
355/S-R	active	397.9, 188.5, 160.9, 92.3

2. In the 8/27/03 "Cellegesic Newsletter," compliance of the study drug/placebo was discussed. The sites were alerted that the ointment may ooze from the tube due to high seasonal room temperatures or by squeezing the tube when the screw cap is on the tube. The newsletter cautioned that this oozing could result in faulty conclusions about dose compliance.
3. A 1 gram weight instead of a 200 gram weight was used to calibrate the scale used to weigh the study drug/placebo. This likely had a low impact on the study drug/placebo weights.
4. One subject randomized to nitroglycerin ointment received a prohibited medication. Subject 041-095 took Panapres 25mg (atenolol) for hypertension and headache (exhibit 13, p. 4). It appears that the sponsor was informed of this protocol violation. However, it is unclear if the sponsor notified the FDA of this protocol violation.

Recommendation: Data from this site were collected in accordance with the protocol. However, the highly variable dose compliance introduces questions regarding the interpretation of the study results. The sponsor's identification that ointment could ooze from the ointment tube when the ointment tube was opened raises uncertainty about the interpretation of the dose compliance numbers.

III. Additional Information from the Inspections

Dr. Stanojevic explained that his country has a relatively high incidence of anal fissures. The country's healthcare system conducts routine health evaluations that identify prospective subjects. Therefore, Dr. Stanojevic did not have difficulty recruiting the relatively large number of subjects.

The FDA Field Investigator asked Drs. Krivokapic and Stanojevic why there was such a dramatic improvement in some subjects' pain, sometimes within 24 hours of enrollment. The CIs did not have any explanations other than they do see this happen and that it could be a placebo effect. There was no indication that the improvement was not an accurate reflection of the subjects' pain relief.

Regarding how the randomization was performed and documented and how the blind was maintained, the sponsor shipped study test article to the investigators in randomized blocks of four kits. The assignment of subjects to the study arms appeared to follow in order of informed consent and other enrollment procedures (i.e. dates of laboratory tests).

Both sites used a subinvestigator dedicated to evaluating healing and who remained blinded to the study treatment. Dr. Stanojevic maintained a separate signed record for each visit from the independent evaluator. The FDA Field Investigator stated that there was no indication that the blind was not maintained.

There were no significant deviations regarding shipping, dispensing to subjects, and final disposition of the study drug.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

I conclude that the overall study data collected by Drs. Krivokapic and Stanojevic were collected in accordance with the protocol. However, the highly variable dose compliance introduces questions regarding the interpretation of the study results. The sponsor's identification that ointment could ooze from the ointment tube when the ointment tube was opened raises uncertainty about the interpretation of the dose compliance numbers.

Mary L. Mease, R.Ph., MPH
Reviewer, Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

Leslie K. Ball, M.D
Branch Chief, Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

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Mary Mease
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Leslie Ball
12/21/04 10:50:17 AM
MEDICAL OFFICER

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: July 19, 2004 DATE OF DOCUMENT: June 30, 2004	DESIRED COMPLETION DATE: October 1, 2004 PDUFA DATE: May 1, 2005	ODS CONSULT #: 01-0097-2
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TO:

Norman Stockbridge, MD
Acting Director, Division of Cardio-Renal Drug Products
HFD-110

THROUGH:

Daryl Allis
Project Manager
HFD-110

PRODUCT NAME:

Cellegesic

(Nitroglycerin Ointment, USP)
0.4%

NDA SPONSOR: Cellegy Pharmaceuticals, Inc.

NDA#: 21-359

SAFETY EVALUATOR: Nora Roselle, PharmD

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Cellegesic. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.
2. DMETS recommends implementation of the labeling and packaging recommendations outlined in section III of this review in order to minimize user error.
3. DDMAC finds the proprietary name, Cellegesic, acceptable from a promotional perspective.

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

**Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 25, 2004
NDA NUMBER: 21-359
NAME OF DRUG: Cellegesic
(Nitroglycerin Ointment, USP)
0.4%
NDA HOLDER: Cellegy Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Cardio-Renal Drug Products (HFD-110), to review the proprietary name, Cellegesic, regarding potential name confusion with other proprietary and established drug names. Insert labeling was provided for review and comment. Container labels and carton labeling were not provided at this time.

PRODUCT INFORMATION

Cellegesic contains 0.4% nitroglycerin ointment. It is indicated for the relief of pain associated with chronic anal fissures. Cellegesic is available in a tube and metered dose-dispensing pump. To obtain a 375 mg dose of ointment from the tube, a finger cot or plastic food wrapped finger is laid alongside the dosing line on the carton. The tube is squeezed until a ribbon of ointment the length of the line is expressed onto the covered finger. The finger is then gently inserted into the anal canal to the first knuckle joint. A metered dose-dispensing pump is also available, dispensing approximately 375 mg of ointment with each depression of the piston. A finger cot is placed on the finger to be used to apply the ointment. The ointment is expelled from the measuring device onto the finger cot and the finger is gently inserted into the anal canal. The dose is to be applied approximately every 12 hours. Since pain relief and healing continue to improve over time, treatment should be continued until the pain abates or up to eight weeks. Cellegesic will be available in 30 gram tubes and 30 gram metered dose dispensers.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Cellegesic to a degree where potential confusion between drug names could occur under the usual clinical practice settings. The Saegis⁴

¹ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, 2004, Facts and Comparisons, St. Louis, MO.

³ The Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, Drugs@FDA, and the electronic online version of the FDA Orange Book.

⁴ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Pharma-In-Use database was searched for drug names with potential for confusion. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written studies with requisition orders and one verbal prescription study, involving healthcare practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel Discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Cellegesic. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have concerns about the name Cellegesic with regard to promotional claims.
2. The Expert Panel Discussion (EPD) and independent investigation identified several proprietary names that were thought to have the potential for confusion with Cellegesic. These products are listed in Table 1 (see below), along with the dosage forms available and usual FDA-approved dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other
Cellegesic	Nitroglycerin Ointment, USP 0.4%	Apply by gently inserting ointment-covered finger into the anal canal to the first knuckle (joint) every 12 hours.	
Cellugel	Ophthalmic Viscosurgical Device supplied in a disposable syringe delivering 2% Hydroxypropyl Methylcellulose (1 mL)	Intraocular use - for use during surgery in the anterior segment of the eye designed to create and maintain space to protect the corneal endothelium and other intraocular tissues during surgery	Look-alike
Allegra	Fexofenadine Tablets: 30 mg, 60 mg, 180 mg Capsules: 60 mg	Adults: 60 mg twice daily or 180 mg once daily Children 6 - 11 years old: 30 mg twice daily	Look-alike
Allegra-D	Allegra-D Tablets: Fexofenadine/Pseudoephedrine (60 mg/120 mg)	Allegra-D: One tablet twice daily	

*Frequently used, not all-inclusive.

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Cellegesic were discussed by the Expert Panel (EPD).

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary names to determine the degree of confusion of Cellegesic with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. A requisition order was written, each consisting of a combination of marketed and unapproved drug products and a prescription for Cellegesic (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, one order was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
OUTPATIENT: <i>Cellegesic 0.2% Sig: apply tid for 1 more week</i>	Cellegesic 0.2% Apply three times daily for one more week.
INPATIENT: <i>Continue Cellegesic 0.2% tid x 1 more week</i>	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. drug product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

1. Look-Alike Concerns

In reviewing the proposed proprietary name Cellegesic, the primary concerns raised were related to look-alike confusion with Cellugel and Allegra.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not always predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to sample size. The majority of misinterpretations were misspelled variations of the proposed name, Cellegesic.

- a. Cellugel was identified to have look-alike similarity with Cellegesic. Cellugel is an ophthalmic viscosurgical device supplied in a disposable syringe delivering 2% hydroxypropyl methylcellulose. Cellugel is for

intraocular use. Cellugel is used during ocular surgery in the anterior segment of the eye and is designed to create and maintain space to protect the corneal endothelium and other intraocular tissues during surgery. Cellugel and Cellegesic have look-alike similarities in that the beginning of each name ('Cellug' vs. 'Celleg') looks alike. However, the endings of each name look different and help to distinguish one name from the other ('el' is shorter than 'esic'). In addition, the two products have several characteristics that help differentiate one product from the other. The two products have different dosage forms (solution vs. ointment), routes of administration (intraocular vs. topical), indications for use (maintains ocular space during eye surgery vs. relief of pain due to anal fissures), and dosing regimens (inserted by a physician during eye surgery vs. applied every 12 hours). In addition, Cellugel is packaged in a sterile, disposable syringe which is a single-use product administered during surgery. We believe that the differences between the two products, as well as look-alike differences when scripted, will help decrease the risk for confusion and error.

Cellugel

Cellegesic

- b. Allegra was identified to have a look-alike similarity with Cellegesic. Allegra (fexofenadine) is an antihistamine used for the relief of symptoms associated with seasonal allergic rhinitis in adults and children six years of age and older. Allegra is available in the following dosage forms and strengths: tablets (30 mg, 60 mg, and 180 mg) and capsules (60 mg). The usual dose of Allegra is 60 mg twice daily or 180 mg once daily. The two names have look-alike characteristics in that the "Ce" in Cellegesic can look like a cursive letter "A". In addition, both names share the letters "lleg". However, when scripted, Cellegesic is longer in length than Allegra and the endings look different ('ra' vs. 'esic'). Both Allegra and Cellegesic may be dosed twice daily. However, the drugs have different dosage forms (tablet and capsule vs. ointment), routes of administration (oral vs. topical), strengths (30 mg, 60 mg, and 180 mg vs. 0.4%), and indications for use. Allegra is available in three different strengths and a differentiating strength would need to be identified prior to filling the prescription unlike Cellegesic (single strength) which does not require a differentiating strength. The differences mentioned above, help differentiate one drug from the other decreasing the likelihood for confusion.

Allegra

Cellegesic

2. Other Safety Related Concerns

Concerns were expressed within DMETS that the "gesic" portion of the name may mislead practitioners to think that this is an analgesic cream, (e.g., for muscle soreness), instead of a pain treatment for anal fissures. Many marketed drug names include the letters 'gesic' (e.g., Co-Gesic, Duragesic, and Norgesic). These products contain well-known pain-relief ingredients such as acetaminophen, hydrocodone, fentanyl, and aspirin. While these products are not all used to treat muscle soreness, they are used to treat various types of pain. Therefore, the potential for confusion is minimal.

III. LABELING, PACKAGING, AND OTHER SAFETY RELATED CONCERNS:

DMETS reviewed the insert labeling for Cellegesic and has identified the following areas of possible improvement. Some comments were detailed in our original review (# 01-0097).

A. CONTAINER LABEL (30 g tube and metered dose pump)

1. The black and white labels provided do not detail the proposed use of color or graphic design. Please ensure that any color or graphic designs used on the labels and labeling do not distract from the type written material.
2. Please ensure that the established name is at least 1/2 the size of the proprietary name as per 21 CFR 201.10(g)(2).
3. The route of administration should be revised to read (b) (4) instead of "For Intra-Anal Use Only". Revise accordingly.
4. As the product is the subject of a USP monograph, we recommend revising the established name as follows: Nitroglycerin Ointment, USP.

B. CARTON LABELING (30 g tube)

1. Please include a statement to the patient warning that the carton should not be discarded as it is the only way the drug dose can be measured.
2. See comments A1 through A4.

C. INSERT LABELING

1. See comments A4 and B1.
2. Precautions, Information for Patients Subsection
 - a. As per 21 CFR 201.57 (f)(2), " Any printed patient information or Medication Guide required under this chapter to be distributed to the patient shall be referred to under the "Precautions" section of the labeling and the full text of such patient information or Medication Guide shall be reprinted at the end of the labeling."
 - b. Information regarding avoiding the use of Cellegesic with Viagra, Levitra, or Cialis should be included in this section so that practitioners can adequately counsel patients on the potential risks of this drug.
3. Dosage and Administration Section
 - a. It is unclear as to whether or not the finger cots will be supplied with drug product. If the finger cots will not be supplied with the drug product, a statement alerting the pharmacist and patient should be provided on the carton labeling. If the latex finger cots are supplied with the drug, a statement stating that they contain latex should be prominently displayed as a number of people have latex sensitivities or allergies.

- b. DMETS believes that the terminology (b) (4) " or (b) (4) is confusing and may lead to error during drug administration. DMETS recommends that patients be encouraged to use finger cots for drug administration.

4. How Supplied Section

Please revise the strength of the product in the HOW SUPPLIED section from 04% to 0.4%.

IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name, Cellegesic. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.
- B. DMETS recommends implementation of the labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name, Cellegesic, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety

APPENDIX A

Verbal	Inpatient	Outpatient
Selagesic	Cellegesic	Cellegesic
Cellagesic	Cellegecic	Cellegesic
Suligesic	Cellegesic	Cellegesic
Selagesic	Cellegecic	Cellegesic
Solagesic	Cellegesic	Cellegesic
Soligesic	Cellegesic	Cellegesic
Cellegesic	Cellegesic	Cellegesic
Solagesic	Cellegesic	Cellegesic
Celagesic	Cellegeric	Cellegesic
Soligesic	Cellegesic	Cellegesic
Celegesic	Cellezecic	Cellegesic
Solagesic	Cellegesic	Cellegesic
Solagesic	Celleziscic	Cellegisc
Celegesic	Cellezecic	Cellegesic
Solugesic	Cellegesic	Cellegesic
Sulgesic	Cellegecic	Cellegesic
Solagesic		Cellegesic
		Cellegesic

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

/s/

Nora L. Roselle
9/24/04 01:10:43 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
9/24/04 01:15:16 PM
DRUG SAFETY OFFICE REVIEWER
Signing for Carol Holquist, Director DMETS

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-359

Trade Name: Cellegesic™ Nitroglycerin Ointment
Generic Name: nitroglycerin
Strengths: 0.4%
Route of Administration Intra-Anal

Applicant: Cellegy Pharmaceuticals, Inc.

Date of Application: June 30, 2004
Date of Receipt: July 1, 2004
Date of Filing Meeting: August 11, 2004
Filing Date: August 30, 2004

Action Goal Date (optional): User Fee Goal Date: May 1, 2005

Indication(s) requested: Relief of pain associated with chronic anal fissure

Type of Original NDA: (b)(1) _____ (b)(2) X

Therapeutic Classification: S X P _____

Resubmission after withdrawal? X

Chemical Classification: (1,2,3 etc.) 3

Form 3397 (User Fee Cover Sheet) submitted: YES

User Fee Status: Paid June 2001 (ID # 4141)

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? NO
- Does another drug have orphan drug exclusivity for the same indication? NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A
If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).
- Is the application affected by the Application Integrity Policy (AIP)?
If yes, explain. NO
- Does the submission contain an accurate comprehensive index? YES
- Was form 356h included with an authorized signature? YES
- Submission complete as required under 21 CFR 314.50? YES

- If an electronic NDA, does it follow the Guidance? YES
Which parts of the application were submitted in electronic format?
Labeling; Publications; Case Report Forms; Clinical Study Report Individual Subject Data
Listings; SAS Datasets
- If in Common Technical Document format, does it follow the guidance? N/A
- Is it an electronic CTD? N/A
- Patent information submitted on form FDA 3542a? YES
The sponsor provided their patent information for Cellegesic with the NDA resubmission documents.
In addition, they provided a letter of commitment, on August 30, 2004, to provide patent certification
for the reference listed drug NDA 20-145 Nitro-Dur.
- Exclusivity requested? NO
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is
not required.*
- Correctly worded Debarment Certification included with authorized signature? YES
- Financial Disclosure forms included with authorized signature? YES
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
- Drug name/Applicant name correct in COMIS? YES
- List referenced IND numbers: 45,326
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
There were numerous meetings and teleconferences between the Sponsor and the Division but none of
them were classified as End-of-Phase 2 or Pre-NDA.
- Pre-NDA Meeting(s)? Date(s) _____ NO

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for
scheduling, submitted? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
The categorical exclusion for the EA was submitted with the original NDA submission.
If no, did applicant submit a complete environmental assessment? N/A
If EA submitted, consulted to Florian Zielinski (HFD-357)? N/A
- Establishment Evaluation Request (EER) submitted to DMPQ? YES

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 11, 2004

BACKGROUND:

Cellegy Pharmaceuticals, Inc. (Cellegy) submitted a new 505(b)2 NDA (NDA 21-359) on June 22, 2001, received June 26, 2001, for Anogesic® (nitroglycerin) 0.2 and 0.4% Ointment intended for use as 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 fissure. The trade name Anogesic was determined to be not acceptable to the Agency and the trade name Cellegesic™ was proposed and found to be acceptable. The NDA was withdrawn on April 25, 2002. Cellegy resubmitted the NDA for Cellegesic™ (nitroglycerin) 0.4% Ointment on June 30, 2004, received July 1, 2004, for the relief of pain associated with chronic anal fissure. This NDA is a resubmission of information included in the original NDA plus the data for an additional clinical trial. Cellegy has requested a deferral for pediatric studies until appropriate studies can be planned and completed in the pediatric population.

ATTENDEES:

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, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Shari Targum, M.D.	Acting Team Leader, Medical Officer, HFD-110
Nhi Beasley, Pharm.D.	Biopharmaceutist, HFD-860
Anthony Proakis, Ph.D.	Pharmacologist, HFD-110
Charles Le Ph.D.	Statistician, HFD-710
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Robert Shibuya, M.D., Ph.D.	Medical Officer, Division of Scientific Investigations, HFD-47
Catherine Miller, MT (ASCP)	Regulatory Review Officer, DDMAC, HFD-42
Daryl Allis, M.S., F.N.P.	Regulatory Health Project Manager, HFD-110

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>	<u>Completion date</u>
Medical:	Dr. Marciniak	October 31, 2004
Secondary Medical:	N/A	
Statistical:	Dr. Le	December 15, 2004
Pharmacology:	Dr. Proakis	August 9, 2004
Statistical Pharmacology:	N/A	
Chemistry:	Dr. Timmer	September 30, 2004
Environmental Assessment (if needed):	N/A	
Biopharmaceutical:	Dr. Beasley	October 31, 2004
DSI:	Dr. Shibuya	October 31, 2004
Regulatory Project Management:	Mr. Allis	
Other Consults:		

Per reviewers, are all parts in English or English translation? YES
If no, explain:

CLINICAL

FILE X

- Dr. Marciniak stated the data are reviewable; there are no filing issues.
- Clinical site inspection needed: YES
Dr. Shibuya stated that domestic sites were inspected during the initial NDA review period.
Dr. Marciniak requested clinical site inspections for 2 sites in Serbia.
- Advisory Committee Meeting needed? NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A

CLINICAL MICROBIOLOGY

NA X

STATISTICS

FILE X

- Dr. Le stated the data are reviewable; there are no filing issues.

BIOPHARMACEUTICS

FILE X

- Dr. Beasley requested that the sponsor provide the assay validation information for the pharmacokinetic study; this, however, is not a filing issue.
- Biopharm. inspection needed: NO

PHARMACOLOGY

FILE X

- Dr. Proakis stated there are no filing issues.

GLP inspection needed:

NO

CHEMISTRY

FILE X

- Dr. Srinivasachar stated there are no filing issues.
- Establishment(s) ready for inspection? Inspection requests have been submitted.
- Microbiology N/A

ELECTRONIC SUBMISSION:

Any comments: The electronic files are reviewable.

Version: 6/16/2004

REGULATORY CONCLUSIONS/DEFICIENCIES:

- The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

ACTION ITEMS:

- Issue an Information Request letter asking the sponsor to submit the assay validation information for the pharmacokinetic study.
- Additional deficiencies and filing issues will be conveyed to applicant by Day 74.

(See appended electronic signature page)

Daryl Allis, R.N., M.S., F.N.P.
Regulatory Project Manager, HFD-110

Draft:	08/31/04	Final:	09/03/04
RD:			
Miller	08/31/04		
Shibuya	09/01/04		
Srinivasachar	09/01/04		
Le	09/01/04		
Proakis	09/01/04		
Beasley	09/01/04		
Targum	09/02/04		
Marciniak	09/02/04		
Karkowsky	09/03/04		
Stockbridge	09/03/04		

**Appendix A to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
NDA 20-145 Nitro-Dur Key Pharmaceuticals, Inc.

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? N/A
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

N/A

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? N/A
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? N/A

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? N/A

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application is for a new indication (pain associated with chronic anal fissure), formulation, and route of administration (intra-anal).

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). NO
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). NO
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). NO

10. Are there certifications for each of the patents listed for the listed drug(s)? NO
The sponsor provided a letter describing their commitment to provide the patent certification for the reference listed drug, Nitro-Dur.

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

_____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

_____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

_____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

 X 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

_____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

_____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

_____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

_____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).?
YES

The cover letter for the application states that Cellegesic Nitroglycerin Ointment 0.4% is 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 fissure.

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4): The sponsor did not request 3-year exclusivity in their cover letter.

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).
YES
- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.
YES
- The number of the applicant's IND under which the studies essential to approval were conducted.
IND # 45,326 YES

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES

Ms. Kim Colangelo, Ms. Virginia Beakes and Ms. Kim Dettelbach were notified in an email dated July 20, 2004.

**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 11:07:08 AM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-359

Trade Name: Cellegesic™ Nitroglycerin Ointment
Generic Name: nitroglycerin
Strengths: 0.4%
Route of Administration Intra-Anal

Applicant: Cellegy Pharmaceuticals, Inc.

Date of Application: June 30, 2004
Date of Receipt: July 1, 2004
Date of Filing Meeting: August 11, 2004
Filing Date: August 30, 2004

Action Goal Date (optional): User Fee Goal Date: May 1, 2005

Indication(s) requested: Relief of pain associated with chronic anal fissure

Type of Original NDA: (b)(1) _____ (b)(2) X
Therapeutic Classification: S X P _____
Resubmission after withdrawal? X
Chemical Classification: (1,2,3 etc.) 3

Form 3397 (User Fee Cover Sheet) submitted: YES

User Fee Status: Paid June 2001 (ID # 4141)

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? NO
- Does another drug have orphan drug exclusivity for the same indication? NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A
- If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).
- Is the application affected by the Application Integrity Policy (AIP)?
If yes, explain. NO
- Does the submission contain an accurate comprehensive index? YES
- Was form 356h included with an authorized signature? YES
- Submission complete as required under 21 CFR 314.50? YES

- If an electronic NDA, does it follow the Guidance? YES
Which parts of the application were submitted in electronic format?
Labeling; Publications; Case Report Forms; Clinical Study Report Individual Subject Data
Listings; SAS Datasets
- If in Common Technical Document format, does it follow the guidance? N/A
- Is it an electronic CTD? N/A
- Patent information submitted on form FDA 3542a? YES
The sponsor provided their patent information for Cellegesic with the NDA resubmission documents.
In addition, they provided a letter of commitment, on August 30, 2004, to provide patent certification
for the reference listed drug NDA 20-145 Nitro-Dur.
- Exclusivity requested? NO
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is
not required.*
- Correctly worded Debarment Certification included with authorized signature? YES
- Financial Disclosure forms included with authorized signature? YES
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
- Drug name/Applicant name correct in COMIS? YES
- List referenced IND numbers: 45,326
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
There were numerous meetings and teleconferences between the Sponsor and the Division but none of
them were classified as End-of-Phase 2 or Pre-NDA.
- Pre-NDA Meeting(s)? Date(s) _____ NO

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for
scheduling, submitted? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
The categorical exclusion for the EA was submitted with the original NDA submission.
If no, did applicant submit a complete environmental assessment? N/A
If EA submitted, consulted to Florian Zielinski (HFD-357)? N/A
- Establishment Evaluation Request (EER) submitted to DMPQ? YES

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 11, 2004

BACKGROUND:

Cellegy Pharmaceuticals, Inc. (Cellegy) submitted a new 505(b)2 NDA (NDA 21-359) on June 22, 2001, received June 26, 2001, for Anogesic® (nitroglycerin) 0.2 and 0.4% Ointment intended for use as 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 fissure. The trade name Anogesic was determined to be not acceptable to the Agency and the trade name Cellegesic™ was proposed and found to be acceptable. The NDA was withdrawn on April 25, 2002. Cellegy resubmitted the NDA for Cellegesic™ (nitroglycerin) 0.4% Ointment on June 30, 2004, received July 1, 2004, for the relief of pain associated with chronic anal fissure. This NDA is a resubmission of information included in the original NDA plus the data for an additional clinical trial. Cellegy has requested a deferral for pediatric studies until appropriate studies can be planned and completed in the pediatric population.

ATTENDEES:

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, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Shari Targum, M.D.	Acting Team Leader, Medical Officer, HFD-110
Nhi Beasley, Pharm.D.	Biopharmaceutist, HFD-860
Anthony Proakis, Ph.D.	Pharmacologist, HFD-110
Charles Le Ph.D.	Statistician, HFD-710
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Robert Shibuya, M.D., Ph.D.	Medical Officer, Division of Scientific Investigations, HFD-47
Catherine Miller, MT (ASCP)	Regulatory Review Officer, DDMAC, HFD-42
Daryl Allis, M.S., F.N.P.	Regulatory Health Project Manager, HFD-110

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>	<u>Completion date</u>
Medical:	Dr. Marciniak	October 31, 2004
Secondary Medical:	N/A	
Statistical:	Dr. Le	December 15, 2004
Pharmacology:	Dr. Proakis	August 9, 2004
Statistical Pharmacology:	N/A	
Chemistry:	Dr. Timmer	September 30, 2004
Environmental Assessment (if needed):	N/A	
Biopharmaceutical:	Dr. Beasley	October 31, 2004
DSI:	Dr. Shibuya	October 31, 2004
Regulatory Project Management:	Mr. Allis	
Other Consults:		

Per reviewers, are all parts in English or English translation?
If no, explain:

YES

Version: 6/16/2004

CLINICAL

FILE X

- Dr. Marciniak stated the data are reviewable; there are no filing issues.
- Clinical site inspection needed: YES
Dr. Shibuya stated that domestic sites were inspected during the initial NDA review period.
Dr. Marciniak requested clinical site inspections for 2 sites in Serbia.
- Advisory Committee Meeting needed? NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A

CLINICAL MICROBIOLOGY

NA X

STATISTICS

FILE X

- Dr. Le stated the data are reviewable; there are no filing issues.

BIOPHARMACEUTICS

FILE X

- Dr. Beasley requested that the sponsor provide the assay validation information for the pharmacokinetic study; this, however, is not a filing issue.
- Biopharm. inspection needed: NO

PHARMACOLOGY

FILE X

- Dr. Proakis stated there are no filing issues.

GLP inspection needed:

NO

CHEMISTRY

FILE X

- Dr. Srinivasachar stated there are no filing issues.
- Establishment(s) ready for inspection? Inspection requests have been submitted.
- Microbiology N/A

ELECTRONIC SUBMISSION:

Any comments: The electronic files are reviewable.

Version: 6/16/2004

REGULATORY CONCLUSIONS/DEFICIENCIES:

- The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

ACTION ITEMS:

- Issue an Information Request letter asking the sponsor to submit the assay validation information for the pharmacokinetic study.
- Additional deficiencies and filing issues will be conveyed to applicant by Day 74.

(See appended electronic signature page)

Daryl Allis, R.N., M.S., F.N.P.

Regulatory Project Manager, HFD-110

Draft:	08/31/04	Final:	09/03/04
RD:			
Miller	08/31/04		
Shibuya	09/01/04		
Srinivasachar	09/01/04		
Le	09/01/04		
Proakis	09/01/04		
Beasley	09/01/04		
Targum	09/02/04		
Marciniak	09/02/04		
Karkowsky	09/03/04		
Stockbridge	09/03/04		

**Appendix A to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
NDA 20-145 Nitro-Dur Key Pharmaceuticals, Inc.

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? N/A
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

N/A

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? N/A
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, N/A
ORP?

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? N/A

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application is for a new indication (pain associated with chronic anal fissure), formulation, and route of administration (intra-anal).

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). NO
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). NO
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). NO

10. Are there certifications for each of the patents listed for the listed drug(s)? NO

The sponsor provided a letter describing their commitment to provide the patent certification for the reference listed drug, Nitro-Dur.

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

_____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

_____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

_____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

X 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

_____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

_____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

_____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

_____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES
 - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
NO
 - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A
 - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).?
YES
- The cover letter for the application states that Cellegesic Nitroglycerin Ointment 0.4% is 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 fissure.

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4): The sponsor did not request 3-year exclusivity in their cover letter.

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).
YES
- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.
YES
- The number of the applicant's IND under which the studies essential to approval were conducted.
IND # 45,326 YES

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES

Ms. Kim Colangelo, Ms. Virginia Beakes and Ms. Kim Dettelbach were notified in an email dated July 20, 2004.

**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 11:07:08 AM
CSO

DSI CONSULT: Request for Clinical Inspections

Date: August 13, 2004

To: Joanne L. Rhoads, M.D., M.P.H., Director, Division of Scientific Investigations, HFD-45
Leslie K. Ball, M.D., Branch Chief, Good Clinical Practice Branch II, HFD-47

Through: Norman Stockbridge, M.D., Ph.D., Acting Director
Division of Cardio-Renal Drug Products, HFD-110

From: Daryl Allis, Regulatory Project Manager
Division of Cardio-Renal Drug Products, HFD-110

Subject: Request for Clinical Inspections
NDA 21-359
Cellegy Pharmaceuticals
Cellegesic (nitroglycerin ointment, 4%)

Protocol/Site Identification:

As discussed with DSI, DCRDP has identified the following sites for inspection.

Indication	Protocol #	Site (Name and Address)
Data Audit	CT 125-03-02-01	Zoran Krivokapic, MD
Data Audit	CT 125-03-02-01	Goran Stanojevic, MD

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

ADD THE FOLLOWING SECTION IF THERE ARE ANY FOREIGN SITES IN THE ABOVE LISTED SITES REQUESTED TO BE INSPECTED:

International Inspections:

We have requested inspections because (please check appropriate statements):

- ☐ There are insufficient domestic data
- ☐ Only foreign data are submitted to support an application
- ☒ Domestic and foreign data show conflicting results pertinent to decision-making

There is a serious issue to resolve, e.g. suspicion of fraud, scientific misconduct, or significant human subject protection violations

Other: The curves of pain scores don't diverge very much and they get a p value of about 0.04 but they've also done some fancy justification of LOCF in individual cases. Their primary analysis is a rate change through day 21 that I haven't check yet. The interesting news is the following:

The day 21 changes in pain scores are marginally different as shown in the following table:

	Summary of Average Pain Change From Baseline at Day 21		
	Mean	Std. Dev.	Freq.
Placebo	-31.164894	21.842101	94
Anogesic	-35.302469	22.442939	81
Total	-33.08	22.155132	175

However, the two largest sites (16 and 20 patients) had among the most favorable results.

Average Change from Baseline at Day 21 / n			
site	Placebo	Anogesic	Total
24	-31.5 10	-44.4 10	-37.95 20
41	-16.1875 8	-35.0625 8	-25.625 16

If these two sites are excluded, the difference in pain scores is virtually gone.

	Summary of Average Pain Change From Baseline at Day 21 Excluding 2 Sites		
	Mean	Std. Dev.	Freq.
Placebo	-32.697368	20.953453	76
Anogesic	-33.888889	22.820379	63
Total	-33.23741	21.747091	139

So, there appears to be strong justification for auditing these two sites.

bsite	invname	country
24	ZORAN KRIVOKAPIC	Serbia
41	ASS. PROF. GORAN STANOJEVIC	Serbia

ADD THE FOLLOWING SECTION IF THERE ARE FIVE OR MORE SITES TO BE INSPECTED:

Five or More Inspection Sites:

N/A

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by **10/29/2004**. We intend to issue an action letter on this application by January 14, 2005.

Should you require any additional information, please contact Daryl Allis, Regulatory Project Manager at (301) 594-5309.

**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
8/26/04 11:18:44 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office): Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 PKLN Rm. 6-34			FROM: Division of Cardio-Renal Drug Products, HFD-110 Dr. Norman Stockbridge, Acting Director Daryl Allis, Project Manager	
DATE July 19, 2004	IND NO.	NDA NO. 21-359	TYPE OF DOCUMENT NDA resubmission	DATE OF DOCUMENT June 30, 2004
NAME OF DRUG Cellegesic		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 3S (New formulation)	DESIRED COMPLETION DATE October 1, 2004
NAME OF FIRM: Cellegy Pharmaceuticals, Inc.				
REASON FOR REQUEST				
I. GENERAL				
☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE/ADDITION ☐ MEETING PLANNED BY ☐ PRE-NDA MEETING ☐ END OF PHASE II MEETING ☐ RESUBMISSION ☐ SAFETY/EFFICACY ☐ PAPER NDA ☐ CONTROL SUPPLEMENT ☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMULATIVE REVIEW ☒ OTHER (SPECIFY BELOW): Trade name review				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):			☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE IV STUDIES			☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL-BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
☐ CLINICAL			☐ PRECLINICAL	
COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: This is a NDA resubmission following withdrawal of the original NDA by the sponsor in April 2002. The trade name Cellegesic is proposed. Please refer to your previous review approving the trade name Cellegesic dated January 8, 2002. The sponsor requested a 6 month review. The Division has determined that the application will receive a standard 10 month review but plans to take an action prior to the May 1, 2005 User Fee Goal date. The draft labeling text is in the EDR filed under the date 30-June-2004. PDUFA DATE: May 1, 2005 ATTACHMENTS: Draft Package Insert, Container and Carton Labels CC: Archival IND 45,326 /NDA 21-359 HFD-110/Division File HFD-110/RPM HFD-110/Reviewers and Team Leaders				
SIGNATURE OF REQUESTER Daryl Allis, Project Manager			METHOD OF DELIVERY (Check one) X MAIL (DFS) ☐ HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

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Daryl L. Allis
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 15, 2002

FROM: Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD 46/7
Division of Scientific Investigations

SUBJECT: Clinical Inspections Summary -- **NDA 21-359**

TO: Edward Fromm, Regulatory Project Manager
Stephen Fredd, M.D., Medical Officer
Division of Cardio-Renal Drug Products, HFD-110

APPLICANT: Cellegy Pharmaceuticals, Inc.

DRUG: Nitroglycerin ointment (Anogesic)

CHEMICAL CLASSIFICATION: 6

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION(S): Relief of pain due to anal fissures

CONSULTATION REQUEST DATE: December 20, 2001

PDUFA GOAL DATE: March 24, 2002

1. BACKGROUND

An anal fissure is a common, benign disease defined as a crack in the anal mucosa. It is associated with intense anal pain and bleeding. Non-surgical therapies include bulk laxatives and sitz baths. Chronic anal fissures are treated surgically.

Anogesic is believed to work by the local conversion of nitroglycerin to nitric oxide which has the effect of relaxing the internal anal sphincter, improving blood flow to the affected area. Previous studies performed by this sponsor suggested accelerated healing with nitroglycerin ointment and improvement in the associated pain.

Protocol NTG 00-02-01 was a multicenter, double-blind, placebo-controlled, dose ranging study with the primary endpoint of pain relief and secondary endpoints of time to healing of the fissure, safety, and quality of life. These three clinical sites were selected on the basis of relatively high enrollment rates.

2. RESULTS (by site):

Name	City	State	IN	Assigned	Action Date	Reviewer	Class
Beck	New Orleans	LA	DA	12/20/01	2/21/02	RBS	NAI
Millis	Columbus	IN	DA	12/20/01	3/14/02	RBS	VAI
Wasvary	Royal Oak	MI	DA	12/20/01	pending	RBS	NAI*

*Per communication with field personnel, no Form FDA 483 was issued. The inspection report has not been reviewed by DSI. Should the review change the classification, this will be communicated to the review division.

David E. Beck, M.D. – Protocol NTG 00-02-01

This site randomized 15 subjects with 13 completing the study. There was no Form FDA 483 issued but minor problems with record keeping were noted. There was no indication of underreporting of adverse events. These data appear acceptable.

Gregory B. Millis, M.D. – Protocol NTG 00-02-01

This site randomized 15 subjects with 14 completing the study. Records for all 15 subjects were reviewed in detail. A Form FDA 483 was issued for minor problems with record keeping. These data appear acceptable.

Harry Wasvary, M.D. – Protocol NTG 00-02-01

This site enrolled 17 subjects with 15 completing the study. Records for all 17 subjects were reviewed. As noted in the summary table, DSI has not reviewed the inspection report. However, communication with the field personnel indicates that no Form FDA 483 was issued. Apparently, there were minor problems with documentation of informed consent, use of a prohibited medication, and the identification of source documents. At this time, it appears that the data from this site is acceptable for review. DSI will notify the review division should this situation change after formal review.

3. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Pending the formal review of the inspection report from Dr. Wasvary's site, no major deficiencies were noted in the three sites inspected that could compromise the integrity of the data. Thus, the data reviewed is acceptable. No subsequent actions or follow up inspections should be undertaken.

Key to Classification:

NAI = No deviation from regulations. Data acceptable.

VAI = Minor deviation(s) from regulations. Data acceptable.

VAI-r = Deviations(s) from regulations, response requested. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable.

Antoine El-Hage, Ph.D.

Associate Director

Good Clinical Practice Branch I & II, HFD-46/7

Division of Scientific Investigations

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/s/

Michele Balser
3/19/02 12:06:03 PM
TECHNICAL
Original signed by Dr. El-Hage.

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
Office of Drug Safety
(ODS; HFD-400)

DATE RECEIVED: 11/30/01	DUE DATE: 01/11/01	ODS CONSULT #: 01-0097-1
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TO: Raymond Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products
HFD-110

THROUGH: Edward Fromm
Project Manager
HFD-110

PRODUCT NAME:
(b) (4), Anogesic (b) (4) and Cellegesic
(Nitroglycerin, USP) Ointment
0.2% and 0.4%

NDA SPONSOR:
Cellegy Pharmaceuticals, Inc.

NDA #: 21-359

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Cardio-Renal Drug Products (HFD-110), the Division of Medication Errors and Technical Support (DMETS) has performed a review of the proposed proprietary names (b) (4), Anogesic (b) (4) and Cellegesic to determine the potential for confusion with marketed drug products and pending drug names.

DMETS RECOMMENDATION: DMETS does not recommend the use of the proprietary names, (b) (4) and Anogesic (b) (4). DMETS has no objection to the use of the proposed third name, "Cellegesic".

This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary name/NDA's/ANDA's from the signature date of this document.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: December 31, 2001

NDA: 21-359

NAME (S) OF DRUG: (b) (4) Anogesic (b) (4) and Cellegesic
(Nitroglycerin, USP) Ointment
0.2% and 0.4%

NDA HOLDER: Cellegy Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult is written in response to a request from the Division of Cardio-Renal Drug Products (HFD-110) for an assessment of the proposed proprietary names, (b) (4) Anogesic (b) (4) and Cellegesic, regarding potential name confusion with other proprietary/generic drug names. DMETS completed a Proprietary Name Review for this product on June 20, 2001 and did not recommend the use of the proprietary name, "Anogesic" (See ODS Consult 01-0097).

PRODUCT INFORMATION

(b) (4) Anogesic (b) (4) Cellegesic contains 0.2% nitroglycerin ointment. It is indicated for the relief of pain associated with chronic anal fissures. A dose-measuring device is provided with each tube of nitroglycerin ointment. The amount of ointment in the measuring device is approximately 374 mg of ointment. A metered dose-dispensing pump is also available, dispensing approximately 374 mg ointment with each depression of the piston. A finger cot is placed on the finger to be used to apply the ointment. The ointment is expelled from the measuring device onto the finger cot and the finger is gently inserted into the anal canal. The dose delivered from the 0.2% ointment is 0.75 mg nitroglycerin and from the 0.4% ointment is 1.5 mg of nitroglycerin. The dose is to be applied two or three times daily until two weeks after the anal pain is gone or the fissure has healed. (b) (4) Anogesic (b) (4) Cellegesic will be available as 0.2% and 0.4% ointment in 30 gm tubes and 30 gm metered dose dispensers.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2,3} as well as several FDA databases⁴ for existing drug names which sound alike or

¹ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

² American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.

³ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

look alike to (b) (4)/Anogesic (b) (4)/Cellegesic to a degree where potential confusion between drug names could occur under usual clinical practice settings. A search of the electronic online version of Thomson and Thomson and the U.S. Patent and Trademark Office's Text and Image Database was also conducted^{5,6}. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted prescription analysis studies consisting of written prescription studies (inpatient and outpatient) and verbal prescription studies, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name (b) (4)/Anogesic (b) (4)/Cellegesic. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The DMETS Expert Panel did not recommend the use of the proposed name, (b) (4) because (b) (4) and Meridia sound and look too similar. The panel also found the proposed name, Anogesic (b) (4) unacceptable, because the panel felt that (b) (4) Anogesic, would not change our previous review; DMETS did not recommend the use of the proprietary name, "Anogesic" (See ODS Consult 01-0097). Therefore, the prescription analysis studies were not conducted for the names, (b) (4) and Anogesic (b) (4).
2. The Expert Panel identified several names that were thought to have the potential for confusion with (b) (4) and Cellegesic.

Product Name	Dosage form(s), Generic name	Usual Dose	Observation
(b) (4)/ Cellegesic	Nitroglycerin ointment: 0.2% and 0.4%	Apply 2 to 3 times daily until 2 weeks after the anal pain is gone or the fissure has healed.	
Meridia (CIV)	Sibutramine HCL: 5, 10, 15 mg capsules	5 to 15 mg po QD.	LA/SA*
Aredia	Pamidronate disodium injection: 30 and 90 mg	Moderate to Severe Hypercalcemia: 60 mg IV over 4 hours or 90 mg IV over 24 hours	SA*
Co-Gesic (CIII)	Hydrocodone 5 mg and Acetaminophen 500 mg tablets	1 to 2 tablets q 4 to 6 hours as needed.	LA/SA*
Celluvisc (OTC)	Carboxymethylcellulose: 1% ophthalmic solution-0.3 mL	1 to 2 drops into affected eye (s) tid to qid.	LA/SA*

*SA = Sound-alike

*LA = Look-alike

3. DDMAC did not have objection to the proposed names, (b) (4), Anogesic (b) (4) and Cellegesic.

B. PRESCRIPTION ANALYSIS STUDIES

⁴ The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

⁵ Data provided by Thomson and Thomson's SAEGISTM Online Service, available at www.thomson-thomson.com.

⁶ WWW location <http://www.uspto.gov/tmdb/index.html>.

1. Methodology:

Three studies were conducted by DMETS involving health professionals comprised of pharmacists, physicians, and nurses within the FDA. The objective was to test the degree of name confusion between Cellegesic and other drug names due to similarity in handwriting and verbal pronunciation of the name. Inpatient and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Cellegesic (see below). These prescriptions were scanned into a computer and subsequently delivered to a random sample of the participating health professionals via e-mail. In addition, the verbal order was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

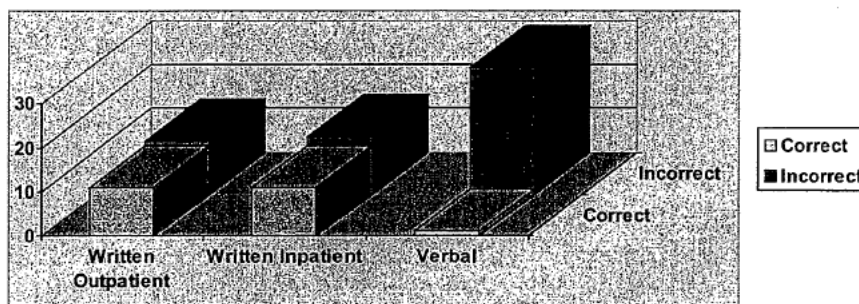
CELLEGESIC

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient Rx: Cellegesic 0.2% Use bid x 4 more days, #1	Verbal Rx: Cellegesic 0.2% Use twice daily for 4 more days. #1
Inpatient Rx: Cellegesic 0.2% bid x 4 more days	

2. The results are summarized in Table I below.

Table I (CELLEGESIC)

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	39	24 (62%)	11 (46%)	13 (54%)
Written Outpatient	34	23 (68%)	11 (48%)	12 (52%)
Verbal	40	30 (75%)	1 (3%)	29 (97%)
Total	113	77 (68%)	23 (30%)	54 (70%)



Among the written prescription study participants for **Cellegesic**, 25 of 47 (53 %) participants interpreted the name incorrectly. Six participants interpreted the name as *Celleges*, four participants interpreted the name as *Cellegeric*, and four participants interpreted the name as *Cellegenic*. Other incorrect responses were *Celligesic*, *Celleges R*, *Cellegest*, *Celligor*, *Celleges M*, *Cellegen*, *Cellegeni*, *Cellergeric*, and *Allergesic*. None of the misinterpretations overlapped with currently approved drug names.

Among the verbal prescription study participants for **Cellegesic**, 29 of 30 (97 %) participants interpreted the name incorrectly. *One participant from the outpatient verbal study interpreted*

the name incorrectly as "Logesic," a name similar to an available product, Co-Gesic. The majority of the incorrect name interpretations were phonetic variations of "Cellegesic." Two participants interpreted the name either as Siligesic, Celogesic, Silagesic, Celegesic, Silogesic, or Selegesic. Other incorrect responses were Solagesic, Fellowgesic, Esilogesic, Eselogesic, Celagesic, Selagesic, Sologesic, Excelogesic, Esalogesic, Aselogesic, Eligestic, Saragesic, Selogesic, Acilogesic, Aseligestic, and Clogesic.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. (b) (4)

(b) (4)

2. (b) (4)

(b) (4)

3. Cellegesic

We conducted prescription studies to simulate the prescription ordering process. In this case, there was a suggestion that Cellegesic could be confused with *Co-Gesic*. *One participant from the outpatient verbal study interpreted the name incorrectly as "Logesic," a name similar to an available product, Co-Gesic.* Other misinterpretations did not overlap with any other currently approved drug names. The majority of the incorrect interpretations of the written and the verbal studies were misspelled/phonetic variations of the proposed name, Cellegesic.

One participant from the outpatient verbal study provided *Logesic* as an interpretation; *Logesic* differs from *Co-Gesic* by one letter. However, the risk of confusion between Cellegesic and *Co-Gesic* is minimal, because Cellegesic and *Co-Gesic* belong to different pharmacological classes and are available in different dosage formulations. *Co-Gesic* contains hydrocodone (5 mg) and acetaminophen (500 mg) tablets while Cellegesic will be available as 0.2% and 0.4% nitroglycerin ointment. Lastly, the two

products have different dosing regimens, further decreasing the risk of medication errors. The usual dose of Co-Gesic is 1 to 2 tablets every 4 to 6 hours as needed and Cellegesic will be applied rectally two to three times daily.

The risk of confusion between *Celluvisc* and Cellegesic is minimal. First, Celluvisc (carboxymethylcellulose sodium) 1% is an over-the-counter (OTC) ophthalmic drug product for persistent dry eye conditions and Cellegesic will be available as rectal ointment for the relief of pain associated with chronic anal fissures. Second, the dosing regimen is very different; Celluvisc is used 1 or 2 drops in the affected eye(s) as needed while Cellegesic ointment is applied rectally two or three times daily. Third, the packaging of the two products is different. Celluvisc lubricant eye drops are supplied in disposable single-use containers of 0.4 mL each while Cellegesic ointment will be available in 30 gm tubes and 30 gm metered dose dispensers. Lastly, the two products will be stored in different areas, further decreasing the risk of medication errors.

DMETS has no objection to the use of the name, Cellegesic.

III. COMMENTS TO BE SUPPLIED TO THE SPONSOR

DMETS does not recommend the use of the proposed proprietary names (b) (4) and Anogesic (b) (4). However, we have no objection to the use of the proprietary name, Cellegesic.

The DMETS Expert Panel did not recommend the use of the proposed primary proprietary name, (b) (4) due to the potential confusion with Meridia. Meridia (sibutramine hydrochloride monohydrate) is an oral agent for the treatment of obesity. Meridia is available as 5 mg, 10 mg, and 15 mg capsules. Meridia does not share overlapping strength, dose, and dosing interval with (b) (4). Although we recognize the differences between these two drug products, we cannot discount the fact that (b) (4) is phonetically and visually very similar to Meridia; (b) (4) differs from *Meridia* by one letter. Therefore, the name, (b) (4), is objectionable in accordance with 21 CFR 201.10(c)(5).

DMETS did not recommend the proposed proprietary name, Anogesic, in our previous consult (ODS consult # 01-0097). The ODS Expert Panel also did not recommend the use of the name, Anogesic (b) (4) because the panel felt that (b) (4), Anogesic, would not change the results of the previous consult.

IV. LABELING, PACKAGING AND SAFETY RELATED ISSUES

See ODS consult number 01-0097.

V. RECOMMENDATIONS:

1. DMETS does not recommend the use of the proposed proprietary names, (b) (4) and Anogesic (b) (4).
2. DMETS has no objection to the use of the proposed proprietary drug name, Cellegesic.

We would appreciate feedback of the final outcome of this consult. We would also be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Hye-Joo Kim at 301-827-3242.

Hye-Joo Kim Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Hye-Joo Kim
1/7/02 03:29:25 PM
PHARMACIST

Carol Holquist
1/7/02 04:07:36 PM
PHARMACIST

Jerry Phillips
1/8/02 07:52:56 AM
DIRECTOR

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: April 25, 2001

DUE DATE:
July 2, 2001

OPDRA CONSULT #: 01-0097

TO: Raymond Lipicky, MD
Director, Division of Cardio-Renal Drug Products
HFD-110

THROUGH: Edward Fromm, Project Manager
HFD-110

PRODUCT NAME:

Anogesic
(Nitroglycerin, USP) Ointment
0.2% and 0.4%

Manufacturer: Cellegy Pharmaceuticals, Inc.

NDA #: 21-359

SAFETY EVALUATOR: Alina R. Mahmud, RPh.

SUMMARY: In response to a consult from the Division of Cardio-Renal Drug Products (HFD-110), OPDRA conducted a review of the proposed proprietary name "Anogesic" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

ODRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name "Anogesic".

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
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Martin Himmel, M.D.
Deputy Director
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Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 20, 2001

NDA NUMBER: 21-359

NAME OF DRUG: Anogesic
(Nitroglycerin, USP) Ointment
0.2% and 0.4%

NDA HOLDER: Cellegy Pharmaceuticals, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Cardio-Renal Drug Products (HFD-110), for assessment of the tradename "Anogesic", regarding potential name confusion with other proprietary/generic drug names. Container and carton labels have not been submitted with this submission.

PRODUCT INFORMATION

Anogesic is the proposed proprietary name for nitroglycerin ointment. Anogesic is indicated for the relief of pain associated with chronic anal fissures. A dose measuring device is provided with each tube of Anogesic ointment. The amount of ointment in the measuring device is approximately 374 mg of ointment. A metered dose dispensing pump is also available, dispensing approximately 374 mg ointment with each depression of the piston. A finger cot is placed on the finger to be used to apply the ointment. The ointment is expelled from the measuring device onto the finger cot and the finger is gently inserted into the anal canal. The dose delivered from the 0.2% ointment is 0.75 mg nitroglycerin and from the 0.4% ointment is 1.5 mg of nitroglycerin. The dose is to be applied two or three times daily until two weeks after the anal pain is gone or the fissure has healed. Anogesic ointment 0.2% and 0.4% will each be available in 30 gm tubes and 30 gm metered dose dispensers.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{i,ii,iii} as well as several FDA databases^{iv} for existing drug names which

ⁱ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

ⁱⁱ American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

sound-alike or look-alike to “Anogesic” to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office’s Text and Image Database was also conducted^v. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name “Anogesic”. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

- The Expert Panel thought that the drug name “Anogesic” sounds too similar to the name “analgesic”.
- Nine product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with Anogesic. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.
- DDMAC objects to use of the proprietary name “Anogesic”. DDMAC found the name “fanciful because it implies that the drug or ingredient has some unique effectiveness or composition when the drug is a common substance, the limitations of which are readily recognized when the drug is listed by its established name.”

TABLE 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Anogesic	Nitroglycerin 0.2% and 0.4% ointment	Apply 2 to 3 times daily until 2 weeks after the anal pain is gone or the fissure has healed.	
Azo-gesic	Phenazopyridine 95 mg tablet (otc)	Two tablets 3 times daily after meals	S/A, L/A per OPDRA
Analgesic	Methylsalicylate and menthol ointment (otc)	Apply to affected area 3 to 4 times daily	S/A, L/A per OPDRA
Argesic	Methylsalicylate and triethanolamine cream (otc)	Not being manufactured at the time. May be discontinued in the near future.	S/A, L/A per OPDRA
Urogesic	Phenazopyridine 100 mg tablet (Rx)	200 mg three times daily with food	S/A, L/A per OPDRA
Equagesic	Aspirin 325 mg, meprobamate 200 mg tablet (CIV-Rx)	1 to 2 tablets 3 to 4 times a day as need	S/A, L/A per OPDRA

ⁱⁱⁱ Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

^{iv} COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

^v WWW location <http://www.uspto.gov/tmdb/index.html>.

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Anogesic	Nitroglycerin 0.2% and 0.4% ointment	Apply 2 to 3 times daily until 2 weeks after the anal pain is gone or the fissure has healed.	
Argesic	Salsalate 500 mg tablet (Rx)	3 gm daily given in 2 or 3 divided doses	S/A, L/A per OPDRA
Amigesic	Salsalate 500 mg tablet (Rx)	3 gm daily given in 2 or 3 divided doses	S/A, L/A per OPDRA
Invagesic	Aspirin 385 mg; Caffeine 30 mg; Orphenadrine 25 mg tablet (Rx)	1 to 2 tablets 3 to 4 times daily	S/A, L/A per OPDRA
Nitroglycerin	2% ointment (Rx)	Apply 1 to 2 inches (25 to 50 mm) every 8 hours, up to 4 to 5 inches (100 to 125 mm) every 4 hours.	S/A, L/A per OPDRA
		*Frequently used, not all-inclusive.	**L/A (look-alike), S/A (sound-alike)

B. STUDY CONDUCTED BY OPDRA

1. Methodology

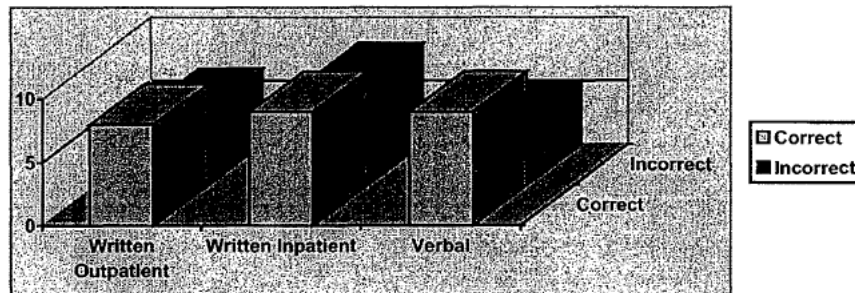
A separate study was conducted within FDA for the proposed proprietary name to determine the degree of confusion of Anogesic with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 86 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Anogesic (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
<i>Outpatient:</i> Anogesic Oint. # 1 Sig: Use BID as directed	Anogesic Ointment Use twice daily as directed Dispense #1
<i>Inpatient:</i> Anogesic ointment BID	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Anogesic" response	Other response
Written: Outpatient	30	14 (47%)	8 (57%)	6(43%)
Inpatient	27	17 (63%)	9 (53%)	8 (47%)
Verbal	28	14 (50%)	9 (64%)	5 (36%)
Total:	85	45 (53%)	26 (58%)	19 (42%)



Among participants in the two written prescription studies, 14 of 31 respondents (45%) interpreted the name incorrectly. The interpretations were misspelled variations of "Anogesic" such as *Amogesic* and *Anegesic*. One participant from the inpatient study interpreted the name as *Analgesic*. Other responses include *Anogesia*, *Angoesic*, *Arogesic*, *Arrogesic*, *Aurogesic*, and *Auogesic*.

Among verbal prescription study participants, 9 out of 14 study participants (64%) interpreted the name incorrectly. Some of the incorrect name interpretations were phonetic variations of "Anogesic" such as *Anugesic*, *Anagesic* and *Energesic*. Five study participants provided the name *Analgesic* as an interpretation.

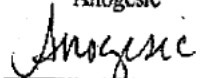
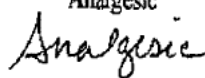
C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Anogesic", the primary concerns raised were related to many sound-alike, look-alike names that already exist in the U.S. marketplace. Eight products, Azogesic, Analgesic, Urogesic, Argesic cream and tablets, Amigesic, Invagesic and Nitroglycerin 2% ointment were believed to be the most problematic in terms of medication error prevention.

OPDRA conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Anogesic could be confused with Analgesic and Argesic. Five study participants from the verbal prescription studies and one participant from the inpatient prescription study provided "Analgesic" as an interpretation. In addition, three participants responded with "Arogesic" and "Arrogesic" which are strikingly similar to the drug name "Argesic". Although there are limitations to the predictive value of these studies primarily due to sample size, we have

acquired safety concerns due to positive interpretations. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

Analgesic is an over-the-counter topical antirheumatic ointment. Analgesic ointment is to be applied to affected areas three to four times daily. Analgesic and Anogesic not only sound similar, the drug names look similar as well (see writing sample below), each beginning with the prefix "An" and ending with the suffix "gesic". Five participants from the verbal prescription study and one participant from the inpatient prescription study interpreted "Anogesic" as "Analgesic". Additionally, Anogesic and Analgesic share an overlapping dosage form (ointment) and dosing schedule (apply three times daily). Although Analgesic ointment is available as an over-the-counter product, some prescribers present patients with written prescriptions for insurance reimbursement purposes. Furthermore, after conducting a search of Thomson and Thomson's database for trademarks and domain names, Analgesic ointment was shown to have a high sales indicator, which demonstrates that this drug is widely used. Moreover, hospital pharmacies stock over-the-counter medications with the prescription medications therefore adding to the potential for confusion. The risks associated with the inadvertent dispensing of Anogesic ointment with Analgesic ointment include mucous membrane irritation and flaring of anal fissures. The risks associated with the inadvertent dispensing of Analgesic ointment with Anogesic ointment include skin irritation and pain associated with lack of treatment. In addition, Anogesic ointment should not be administered to patients who are concomitantly using sildenafil citrate (Viagra).

Anogesic	Analgesic
	

Argesic is the proprietary name for an over-the-counter antirheumatic cream, which contains

(b) (4). Argesic cream is not currently being manufactured (b) (4). However, Argesic continues to appear in widely used and easily accessible reference texts. Post-marketing experience has demonstrated medication errors occurring as a result of drug names appearing in reference texts even though the products may no longer be available. Anogesic and Argesic differ by only two letters and are both used topically, therefore, having a high potential for confusion. In addition, three participants the written inpatient prescription study responded with "Arogesic" and "Arrogesic" which are strikingly similar to the drug product "Argesic".

Azo-gesic, Urogesic, Invagesic, Argesic and Amigesic are all available in solid oral dosage forms. Although post-marketing experience has not demonstrated medication errors occurring between oral and topical preparations, one can not overlook the look-alike and sound-alike similarity in name between these drugs and Anogesic. In addition, these products share an overlapping dosing schedule with Anogesic (three times daily).

OPDRA has safety concerns with the approved drug product nitroglycerin 2% ointment and the proposed nitroglycerin 0.2% ointment. Both products share a similar numerical strength (2% vs. 0.2%) and dosage form (ointment). Post-marketing experience has demonstrated errors occurring as a result of practitioners omitting the leading zero when expressing the strength of the product.

In addition, both products will be stored in the same area, possibly adjacent to one another. Therefore, in order to minimize confusion between the two products, OPDRA recommends that the sponsor utilize the container and carton label to differentiate the two products. More specifically, the strength should be displayed prominently with contrasting colors.

DDMAC objects to use of the proprietary name "Anogesic". DDMAC found the name "fanciful because it implies that the drug or ingredient has some unique effectiveness or composition when the drug is a common substance, the limitations of which are readily recognized when the drug is listed by its established name."

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the draft package insert, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified one area of possible improvement, in the interest of minimizing potential user error.

A. Container Label

Please provide for evaluation.

B. Carton labeling

Please provide for evaluation.

C. Device(s)

Please provide for evaluation.

D. Package Insert

1. It is unclear as to whether or not the finger cots will be supplied with drug product. If the finger cots will not be supplied with the drug product, a statement alerting the pharmacist and patient should be provided on the carton labeling.
2. We note that the instructions for use for the measuring device are included only. Patient instructions should also be included for the metered dosing device. Each set of instructions should be clearly labeled as to which device is provided with the packaging and which instructions should be followed. In addition, it is important to inform patients of the varying dispensers, in case they receive one or the other at different times when requesting refills.
3. The ointment application instructions for the non-metered dosing device do not clearly state whether the entire device contents should be expelled onto the finger cot. The inclusion of explicit directions for use is recommended so that patients may accurately and safely administer the medication.

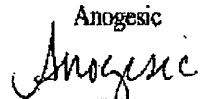
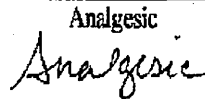
4. As per 21 CFR 201.57 (f)(2), “ Any printed patient information or Medication Guide required under this chapter to be distributed to the patient shall be referred to under the “Precautions” section of the labeling and the full text of such patient information or Medication Guide shall be reprinted at the end of the labeling.”

IV. COMMENTS TO BE PROVIDED TO THE SPONSOR

In reviewing the proprietary name "Anogesic", the primary concerns raised were related to many sound-alike, look-alike names that already exist in the U.S. marketplace. Eight products, Azo-gesic, Analgesic, Urogesic, Argesic cream and tablets, Amigesic, Invagesic and Nitroglycerin 2% ointment were believed to be the most problematic in terms of medication error prevention.

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Anogesic	Analgesic
	

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(b) (4)

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(b) (4)

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V. RECOMMENDATIONS

OPDRA does not recommend the use of the proprietary name "Anogesic".

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, R.Ph. at 301-827-3231.

Alina R. Mahmud, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

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

/s/

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6/29/01 09:17:42 AM
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DIRECTOR

Martin Himmel
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