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*APPLICATION NUMBER:*

**21-359**

**OTHER ACTION LETTER(s)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 021359

**COMPLETE RESPONSE**

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

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

Dear Dr. Norvitch:

Please refer to your new drug application (NDA) dated June 22, 2001, received June 26, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for nitroglycerin 0.4% ointment.

We acknowledge receipt of your amendment dated September 30, 2009, and March 10, 2010.

The September 30, 2009, amendment constituted a complete response to our July 7, 2006, action letter.

We also acknowledge receipt of your amendments dated January 14 and March 17, 2010, which were not reviewed for this action. You may incorporate applicable sections of the amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

#### **CLINICAL**

1. In July of 2006, the Division of Cardiovascular and Renal Products notified you that, prior to approval of this drug, you would have to perform another trial in patients with chronic anal fissure demonstrating improvement in anal pain at the usual level of statistical significance ( $p < 0.05$ ). In response to this deficiency, you conducted and submitted Study REC-C-001, a randomized, double-blind, placebo-controlled, parallel-group study. Upon review, we have determined that Study REC-C-001 failed to demonstrate efficacy because the pre-specified, conservative analysis did not yield a statistically significant difference for the primary endpoint.

Information needed to address Deficiency 1:

Conduct and submit an adequate and well-controlled trial to support the efficacy of this product. Per our previous advice to you, the statistical analysis should use a conservative method to impute data for patients who discontinue early.

**NONCLINICAL**

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

Information needed to address Deficiency 2:

You must provide evidence that, under conditions of maximal administration as labeled, your product produces exposure levels to nitroglycerin and its metabolites that are within the same range as one or more Reference Listed Drugs approved for repeated or chronic use. Failure to provide this support in a future resubmission of the application will result in the following additional requirements:

- a. Sufficient clinical experience provided to support the local and systemic safety of the human exposure at the maximal dosing regimen, or additional repeat-dose toxicology studies using the intra-rectal route in two species (one non-rodent) up to a chronic duration.
- b. Adequate nonclinical toxicokinetic bridging studies with dietary or topical exposure as appropriate to establish safety margins for animal reproductive toxicology and carcinogenicity studies to be described in the label.
  - (1) Should bridging studies fail to establish adequate exposure to nitroglycerin and its metabolites to support a risk assessment you will need to conduct new reproductive toxicology studies with routes that produce sufficient exposures to allow an adequate risk assessment.
  - (2) Should bridging studies fail to establish adequate exposure to nitroglycerin and its metabolites to support a risk assessment, and if you do not provide usage data or other persuasive arguments to indicate that this product should not be considered a chronic use (i.e. >6 months lifetime usage) product, you will need to conduct a carcinogenicity evaluation with routes that produce sufficient exposures to allow an adequate risk assessment.

## PRODUCT QUALITY

3. You have not adequately demonstrated comparability of the drug product quality from the proposed commercial manufacturing site ( (b) (4) ) to the clinical site ( (b) (4) ).

### Information needed to address Deficiency 3:

A minimum of three months stability data is required for your registration batches at long-term storage conditions (25°C/60%RH), intermediate storage conditions (30°C/65%RH), and accelerated storage conditions (40°C/75%RH) to bridge your primary ( (b) (4) ) and supportive ( (b) (4) ) stability data and establish an expiry period. Submit all available stability data for these batches (906493-0, 906494-0, and 906495-0).

In addition, you must address the following CMC deficiencies pertaining to critical quality attributes of your drug product:

4. Establish validation criteria for resolution between the impurities in the (b) (4) analytical method for impurities.
5. Establish a viscosity specification of NLT (b) (4) cps at release and between (b) (4) and (b) (4) cps upon stability.
6. Tighten your proposed drug product specifications for the (b) (4) to reflect your current manufacturing process capabilities and stability data.
7. ProStrakan Study Report 4, "Preparation of further lab-scale batches of Rectogesic® ointment 0.4%" clearly demonstrates the dependence of the drug product viscosity on the (b) (4). Propose acceptance criterion for (b) (4) with justification of this acceptance criterion. Your justification should demonstrate the ability to control the drug product viscosity through the proposed expiry period.
8. ProStrakan Study Report 4, "Preparation of further lab-scale batches of Rectogesic® ointment 0.4%" references Report 40002-1135-0509 for information regarding the variance in *in vitro* drug release rates related to formulations using different vendors for excipients. Provide this report and conclusions regarding the components that affect *in vitro* release rate. Establish appropriate quality control strategies to control these components.

## LABELING

9. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling

[21 CFR 314.50(I)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We refer to our August 26, 2004, letter granting a deferral of pediatric studies in patients ages <1 to 16 years of age for nitroglycerin 0.4% ointment for relief of pain associated with chronic anal fissure. These pediatric studies were deferred for your application under 21 CFR 314.55 until May 1, 2007.

We also refer to your request for waiver in patients (b) (4) years of age and your request for a deferral in patients (b) (4) years of age submitted in your September 9, 2009, amendment.

It may be possible to waive studies in pediatric patients under the age of (b) (4) years. Commence pediatric studies and submit final study reports with your NDA resubmission. Pediatric studies must include an assessment of safety, pharmacokinetics, and efficacy.

## SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

#### **OTHER**

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

*{See appended electronic signature page.}*

Rigoberta Roca, MD  
Deputy Director  
Division of Anesthesia and Analgesia and Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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

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/s/

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RIGOBERTO A ROCA  
03/30/2010



NDA 21-359

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

Dear Dr. Azarnoff:

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

We acknowledge receipt of your submissions dated January 27 (2), February 28, April 14, 25, 2005, January 31 and May 22, 2006. The April 14, 2005 submission constituted a complete response to our December 23, 2004 action letter.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to perform another trial with Cellegesic Ointment in patients with chronic anal fissure demonstrating improvement in anal pain at the usual level of statistical significance ( $p < 0.05$ ). We are requiring the additional study because we believe the results of the three randomized trials conducted to date do not provide substantial evidence that the drug is effective. The first study clearly failed to show an effect on its primary endpoint of improving anal fissure healing. 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 specified in the protocol.

The evidence of benefit thus depends very much on the results of the third study. The first two studies could provide some support, but only if the third study is "strongly supportive". The following considerations render the third study even less persuasive in our view than your calculated  $p = 0.0498$  would convey.

1. The treated group had all of the early withdrawals because of headaches. Ordinarily, in a study that uses a last observation carried forward analysis, the group with more early withdrawals for adverse effects is disadvantaged because the early values do not benefit from late spontaneous improvement. This study examined the rate of change in pain, but this analysis too, would give a disadvantage to the group with more dropouts, if the dropouts' slope were based on the last measured value carried forward, again because the late slope would not reflect the observed spontaneous improvement. There is one analysis, however, that gives great advantage to the group with early dropouts—a rate of change analysis that uses observed values up to the time of dropout. In this case, the slope for the dropouts is dominated by the early rapid changes seen in both the drug and placebo, which probably represents regression to the mean, but in any case does not represent drug effect. For your third study, only analyses that treat some or all

dropouts this way give nominally significant results. We consider this a biased analysis inevitably favoring the treatment group, which had all the early dropouts, whether or not the decision to use this analysis was made in a blinded state.

2. We interpret the protocol specified analysis as calling for all subjects who discontinued because of headache to have their last observation carried forward. This changes the handling of 3 subjects' data and results in  $p = 0.12$ .
3. We are also concerned that the small nominal treatment effect may be attributable to unbalanced use of acetaminophen.
4. Finally, we note that the favorable trend appears to be confined to the subjects in Serbia, with no favorable trend at all in the other participating countries, a major problem given that this is the most critical study and that the drug is intended for use in the United States.

Thus, we do not believe the results of this study support the effectiveness of Cellegesic when it is appropriately analyzed. We believe an additional study is needed.

We suggest that the additional study make use of suggestions in the available data by enrolling a potentially more responsive population. Based on your analysis of effect by stratum of baseline pain score, you may wish to enroll patients with a high qualifying score. We also suggest that you have separate baseline and qualifying scores to avoid some of the regression to the mean phenomenon. As the slope analysis is particularly strongly affected by early dropouts, we strongly recommend that you use pain at some time (e.g., 2 weeks) or the integral of pain over some time and not rate of change in pain as this study's primary end point. You should also consider how to remove concerns about differences in background analgesic use, either by forbidding it or by mandating a standard regimen. The statistical analysis plan should be finalized before much of the data are acquired.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Cardio-Renal Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

*{See appended electronic signature page}*

Robert Temple, M.D.  
Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Robert Temple  
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-359

Cellegy Pharmaceuticals, Inc.  
Attention: Daniel L. Azarnoff, M.D., F.A.C.P.  
349 Oyster Point Boulevard, Suite 200  
South San Francisco, CA 94080-1913

Dear Dr. Azarnoff:

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

We acknowledge receipt of your submissions dated September 3, 21, 28, & 30, October 5, 6, 22, & 26, November 3 & 19, and December 14, 21, & 22, 2004.

We have completed our review of your submissions and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. At best, the difference between the nitroglycerin ointment and placebo groups was 3 mm (out of 100) mean change from baseline in the average anal pain visual analog scale in study 03-02-01, only about 13% of the placebo effect. This small effect estimate does not balance favorably against a high rate of withdrawals for headache and other adverse effects with nitroglycerin ointment.
2. Several observations suggest that even this modest effect may be an overestimate of the effectiveness of nitroglycerin ointment.
  - The first two studies only showed effects on anal pain that were nominally statistically significant using retrospective analyses. Your confirmatory study, when analyzed by the protocol-specified linear mixed-effects regression model using last observation carried forward for all nitroglycerin patients who withdrew because of headache, failed to demonstrate a statistically significant improvement in the rate of change of average daily pain through 21 days, the primary endpoint.
  - Not counting the two patients in each treatment group at the disqualified site, eleven patients randomized to nitroglycerin ointment in the third study failed to complete 21 days while no patients randomized to placebo failed to complete 21 days. This large imbalance in withdrawals between the two groups makes it difficult to interpret any differences in results between the two groups over the primary endpoint evaluation period of 21 days.
  - Concomitant use of acetaminophen was also more common with nitroglycerin than with placebo, making it difficult to ascribe any small pain relief to nitroglycerin.

3. In any future resubmission, please also respond to the following issues:
- In the third study one nitroglycerin ointment patient withdrew because of dizziness, bradycardia, and extrasystoles and another withdrew because of tachycardia, both adverse events suggestive of systemic cardiovascular adverse effects of nitroglycerin absorption and both inadequately documented.
  - Vital sign changes following chronic administration of nitroglycerin ointment and the variability thereof are also inadequately documented in the application.
  - The pharmacokinetic study included in the application documented about 50% bioavailability of nitroglycerin with wide variability (range 8-99%).

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Cardio-Renal Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please contact:

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

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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