CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-359

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	June 21, 2011
From	Rigoberto Roca, M.D.
Subject	Deputy Director Summary Review
NDA/Supplement No.	21-359
Applicant Name	ProStrakan, Inc.
Date of Original Submission	June 22, 2001
Date of Complete Response	December 23, 2004; July 7, 2006; March 30, 2010
Date of Re-Submission	December 21, 2010
PDUFA Goal Date	June 21, 2011
Proprietary Name / Established (USAN) Name	Rectiv / Nitroglycerin 0.4% ointment
Dosage Forms / Strength	Ointment / 0.4% w/w
Proposed Indication	Treatment of moderate to severe pain associated with a chronic anal fissure.
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Neville Gibbs, M.D., M.P.H.
Statistical Review	Yongman Kim, Ph.D. / Dionne Price, Ph.D.
Pharmacology Toxicology Review	Newton Woo, Ph.D. / Adam Wasserman, Ph.D.
Chemistry, Manufacturing, and Controls Review (ONDQA)	Olen Stephens, Ph.D. / Prasad Peri, Ph.D. Tapash Ghosh, Ph.D. / Patrick Marroum, Ph.D.
Clinical Pharmacology Review	David Lee, Ph.D. / Yun Xu, Ph.D.
OSE/DMEPA	Manizheh Siahpoushan, Pharm.D. / Zachary Oleszczuk, Pharm.D. / Kellie Taylor, Pharm.D., M.P.H. / Todd Bridges, R.Ph.
DDMAC	Mathilda Fienkeng / Latoya S. Toombs

CDTL = Cross-Discipline Team Leader
DDMAC = Division of Drug Marketing, Advertising and Communications
DMEPA = Division of Medication Error Prevention and Analysis
OND = Office of New Drugs
ONDQA = Office of New Drug Quality Assessment
OSE = Office of Surveillance and Epidemiology

1. Introduction

The applicant, ProStrakan, Inc., submitted the results of a Phase 3 study with their nitroglycerin ointment (0.4% w/w), on September 30, 2009, in support of a 505(b)(2) application for the treatment of pain associated with chronic anal fissures. That submission constituted a Complete Response to an Approvable action taken by the Agency on July 7, 2006. The conclusion at the end of that review cycle was the Applicant had been unsuccessful in demonstrating the effectiveness of the nitroglycerin ointment for the desired indication, and a Complete Response letter was issued on March 30, 2010.

The current submission is the Applicant's attempt to address the concerns and deficiencies identified in the March 30, 2010 letter, incorporating the advice given to the Applicant during the dispute resolution process.

The regulatory history of this application involves several review cycles, changes in the application's sponsor, and a request for formal dispute resolution. This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history and the adequacy of the data to support the application.

2. Background

Nitroglycerin is an organic nitrate with vasodilator properties that has been clinically used extensively for the treatment of angina. Its use in the treatment of pain in the anorectal region associated with anal fissures has been reported in many clinical journals. Although the immediate cause of anal fissures may differ, there is usually an associated spasm of the internal anal sphincter that at times is so severe that blood flow to the muscle may be impeded. The hypothesis that the perceived pain may be ischemic in nature offers a potential role for nitroglycerin therapy.

The regulatory history of this application spans almost ten years, and is well-documented in the reviews by the review team, and in my memo of March 30, 2010. In brief, the most important milestones are noted below.

- June 22, 2001 – the original application is submitted by Cellegy Pharmaceuticals to the Division of Cardio-Renal Products (DCRP), with two Phase 3 studies intended to demonstrate efficacy for pain relief and healing of anal fissures. The application was withdrawn on April 25, 2002, prior to the official Agency action.
- June 30, 2004 – the NDA was resubmitted to DCRP with the results of a new Phase 3 study. The application received a Not Approvable action on December 30, 2004.
- April 14, 2005 – Cellegy Pharmaceutical submitted a complete response to DCRP, consisting of a re-analysis of the data from the Phase 3 studies. An advisory committee meeting was held on April 26, 2006, and the final recommendation from the twelve voting members was an even split between approval and non-approval. The division took an Approvable action on July 7, 2006. Among the items cited in the action letter was the need for another Phase 3 study that would demonstrate the product's effectiveness.

- May 22, 2007 – a Type A meeting was held between ProStrakan, Inc., which had acquired the application from Cellegy Pharmaceutical the previous November, and the Division of Anesthesia, Analgesia, and Rheumatology Products, the division to which regulatory oversight for this application had been transferred. The major outcomes from this meeting were:
    - The three previously conducted Phase 3 trials had failed to demonstrate the efficacy of the product as a treatment for pain due to anal fissures.
    - An additional Phase 3 trial would be necessary.
    - Patient selection, specifically enrollment of patients with moderate to severe pain secondary to chronic anal fissures, may address concerns about regression to the mean.
    - The primary endpoint could be pain at a specific time point, or an integral of pain over time.
- September 30, 2009 – The Applicant submitted the results of Study REC-C-001, which was initiated in August of 2007. It was a multicenter, randomized, double-blind, parallel-group trial conducted in the United States and Latin America, in adult patients with moderate to severe pain (i.e., a score of at least 50/100 mm on a visual analog scale) due to a chronic anal fissure. The application received a Complete Response on March 30, 2010.
- June 17, 2010 – Post-Action meeting held with Applicant.
- August 25, 2010 – Formal Dispute Resolution Request submitted by Applicant.
- September 22, 2010 – Appeal denied by Dr. Rosebraugh, Director of Office of Drug Evaluation (ODE) II; the denial letter contained advice on potential statistical analyses that could be performed on the data from Study REC-C-001 which could provide a possible path forward to resolve the deficiencies identified in the March 30, 2010 letter.

This submission constitutes the Applicant's re-analysis of the data from Study REC-C-001, incorporating the advice given in the September 22, 2010 letter. Specifically, as noted in Dr. Gibb's and Dr. Kim's review, and further elaborated below in this review, the new analyses were intended to evaluate different imputation strategies to address missing data.

3. Chemistry, Manufacturing, and Controls (CMC)

During the last review cycle, it was noted that the Applicant had changed the drug product manufacturer to (b) (4) but had not submitted sufficient stability data to bridge the drug product registration batches to batches from the previous drug product manufacturer. Due to this deficiency, the recommendation from Dr. Stephens, the CMC reviewer, was for the application to not be approved.

The noted deficiency has been adequately addressed in this submission, and a shelf life of 18 months has been granted for the drug product when stored under the labeled conditions of 20°-25°C (68°-77°F); excursions will be permitted between 15°-30°C (59°-86°F).

I concur with the conclusions reached by Dr. Stephens and the rest of the ONDQA review team that, from a CMC perspective, the application can be approved.

4. Nonclinical Pharmacology/Toxicology

During the last review cycle, as noted in Dr. Leshin's and Dr. Wasserman's review and summarized in my previous memo, the majority of the nonclinical literature information supporting the marketing of nitroglycerin was based on dietary administration of nitroglycerin, which may not have reflected the same exposure as topical administration due to the expected hepatic first-pass effect expected with oral administration of the product. Further, the review team concluded during the previous review cycle that the referenced drug cited by the Applicant, Nitro-Dur, did not provide adequate coverage for the exposure anticipated with the proposed formulation.

As noted by Dr. Woo in his review, the Applicant submitted literature information in the meeting briefing package for the June 17, 2010 meeting, and a subsequent information amendment, which provided evidence that use of the 0.4% nitroglycerin ointment as proposed by the Applicant would result in exposure levels of nitroglycerin and its metabolites which fall within those reported with Nitro-Dur. This information was deemed adequate by the Clinical Pharmacology reviewers and Pharmacology/Toxicology Staff; consequently the Applicant has adequately addressed this deficiency.

The other nonclinical issue identified during the last review cycle was whether the use of the nitroglycerin ointment for this indication could constitute "chronic use," thereby necessitating the need for carcinogenicity studies. I noted in my memo that, although I agreed with Drs. Gibbs and Shibuya that the number of patients that may use the product in a chronic fashion may be small, it was up to the Applicant to provide the data to make the argument that carcinogenicity studies were not required.

After additional internal discussions and re-evaluation of the pathophysiology of the intended indication, it was concluded that the anticipated use of this product would not meet the criteria that would be defined as chronic use and that, therefore, carcinogenicity studies were not required. Subsequently, this was not identified as a deficiency in the March 30, 2010 Complete Response letter.

I concur with the conclusions reached by Dr. Woo and Dr. Wasserman that, from a pharmacology/toxicology perspective, there are no outstanding issues that would preclude approval of this application.

5. Clinical Pharmacology/Biopharmaceutics

There was no new clinical pharmacology data submitted in this application. I concur with the conclusions reached by Dr. Lee and Dr. Xu that there are no outstanding clinical pharmacology issues that preclude approval of this application.

6. Clinical Microbiology

The nitroglycerin ointment is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical – Efficacy

The Applicant did not submit any new efficacy data, only a reanalysis of the data from the previously submitted Phase 3 clinical trial, Study REC-C-001. The details of the trial design are well-described in the reviews by the clinical and statistical members of the review team and in my previous memo.

In brief, Study REC-C-001 was a multicenter, randomized, double-blind, parallel-group trial in adult patients (age 18 to 75 years) with moderate to severe pain (i.e., a score of at least 50/100 mm on a visual analog scale) of at least six weeks duration prior to the screening visit, due to a chronic anal fissure. It was conducted in clinical sites in the Argentina, Brazil, Mexico, and United States.

The primary efficacy endpoint of the trial was the change from baseline in the 24-hour average pain intensity, as determined by a patient-reported score using the visual analog scale (VAS), averaged over Days 14 to 18 of treatment.

A total of 247 patients were randomized and 219 completed the trial. The demographics and baseline characteristics between the two treatment groups were comparable. The disposition of the patients is summarized in the table below, adapted from Dr. Kim's review.

	Nitroglycerin 0.4% ointment N=123 n (%)	**Placebo** N=124 n (%)	**Total** N=247 n (%)
Total number of patients			
Completed	106 (86.2)	113 (91.1)	219 (88.7)
Discontinued	17 (13.8)	11 (8.9)	28 (11.3)
Primary reason for discontinuation			
Adverse event	9 (7.3)	3 (2.4)	12 (4.9)
Voluntary withdrawal	5 (4.1)	4 (3.2)	9 (3.5)
Protocol violation	2 (1.6)	0	2 (0.8)
Lost to follow up	1 (0.8)	4 (3.2)	5 (2.0)

The results for the primary efficacy endpoint for the ITT population, defined as all randomized patients who had taken at least one dose, are summarized in the table below, adapted from Dr. Kim's review from the previous review cycle.

LS Mean Change (SE) from Baseline to average of Days 14 to 18 in 24-hour average pain	**Nitroglycerin 0.4% ointment (N=123)**	**Placebo (N=124)**	**P-value**
ANCOVA/BOCF*	-40 (3.1)	-35 (3.0)	0.118
Difference from Placebo (SE) (95% CI)	-5 (3.5) (-12, 1)		

*P-value calculated from ANCOVA model with terms for treatment, region, gender, and baseline score as a covariate.

The prespecified analysis of the primary efficacy endpoint stipulated an imputation strategy of baseline-observation-carried-forward (BOCF) for missing data, as conveyed to the Applicant by the Division during the May 22, 2007 Type-A meeting.

The Applicant also submitted results from two sensitivity analyses performed using a last-observation-carried-forward (LOCF) imputation strategy. The first, designated as LOCF 1, was pre-specified before unblinding of the randomization code, and imputed missing data from the last non-missing observation, whether it fell before Day 18 (last day of primary pain assessment) or not. The second analysis, designated as LOCF 2, was proposed after unblinding of the randomization code, and it restricted imputation from the last non-missing observation before Day 18. The results from these two analyses are summarized in the two tables that follow, adapted from Dr. Kim's review from the previous review cycle.

LOCF 1: REC-C-001 (ITT Population)

LS Mean Change (SE) from Baseline to average of Days 14 to 18 in 24-hour average pain	**Nitroglycerin 0.4% ointment (N=123)**	**Placebo (N=124)**	**P-value**
ANCOVA/LOCF 1*	-37 (3.0)	-30 (3.1)	0.047
Difference from Placebo (SE) (95% CI)	-7 (3.4) (-13, 0)		

*P-value calculated from ANCOVA model with terms for treatment, region, gender, and baseline score as a covariate.

LOCF 2: REC-C-001 (ITT Population)

LS Mean Change (SE) from Baseline to average of Days 14 to 18 in 24-hour average pain	**Nitroglycerin 0.4% ointment (N=123)**	**Placebo (N=124)**	**P-value**
ANCOVA/LOCF 2*	-36 (2.9)	-29 (3.0)	0.033
Difference from Placebo (SE) (95% CI)	-7 (3.4) (-14, -1)		

*P-value calculated from ANCOVA model with terms for treatment, region, gender, and baseline score as a covariate.

As noted in Dr. Kim's review from the previous review cycle, a LOCF analysis may potentially provide supportive information only when a conservative analysis provides significant results. Since the conservative analysis utilizing a BOCF imputation strategy failed, the significance of a favorable LOCF analysis was questionable. Since the Applicant had failed to demonstrate the product to be effective compared to placebo, utilizing the prespecified analysis on the primary endpoint, I concurred with the review team that the application could not be approved.

As noted in Dr. Kim's review, the Applicant posited that the baseline-observation-carried-forward imputation method for the handling of missing data in the primary analysis was potentially overly conservative in this situation, due to the nature of the progression of anal fissures. If a patient dropped out of the trial because they experienced pain relief prior to the pre-specified timepoint in the trial at which effectiveness was to be assessed, and if a baseline score would be imputed, then the imputed score would not accurately reflect the true outcome.

In their request for a Formal Dispute Resolution, they petitioned for the opportunity to utilize a different imputation method than BOCF.

In his response to the Applicant's request for a dispute resolution, Dr. Rosebraugh proposed two approaches that the Applicant could try to address the issue of missing data: a retrieved-dropout methodology, and a LOCF/BOCF hybrid methodology. Dr. Rosebraugh noted in his letter that the considerations for further imputation strategies were unique to the situation in this application and not necessarily applicable to other applications. Specifically, he identified the nature of the disease (high rate of spontaneous resolution), low placebo drop-out rate, and limited use of rescue therapy as conditions that permitted this particular path forward.

The Applicant incorporated Dr. Rosebraugh's advice by defining the types of imputation they would utilize in the analyses in the following manner:

1. Retrieved-dropout analysis:
    a. Patients who withdrew but had at least one pain score assessed during Days 14-18 and had not taken rescue medication were considered retrieved dropouts. The average score during Day14 to Day 18 was imputed for these patients.
    b. The baseline scores were imputed for all other dropouts.

2. LOCF/BOCF hybrid analysis:
    a. A potentially "good" score (LOCF) was imputed for patients who withdrew but demonstrated an early effective pain relief.
    b. If such patients were also retrieved-dropouts, then the average score during Day14 to Day 18 was imputed.
    c. For other dropouts, baseline scores were imputed (BOCF).
    d. Three blinded reviewers of the Data Review Committee independently evaluated dropouts and applied a majority rule to adjudicate dropouts with early effective pain relief.

The results of the LOCF/BOCF hybrid analysis were as follows (adapted from Dr. Kim's review):

VAS Score	**Nitroglycerin ointment 0.4% (N=123)**	**Placebo (N=124)**
Actual Baseline Mean (SD)	73 (14.5)	73 (13.2)
Actual Day 14-18 Mean (SD)	31 (26.6)	38 (27.8)
Change from Baseline Adjusted Means (SE)	-44 (3.0)	-37 (3.0)
Difference from placebo (SE) 95% CI	-7 (3.3) (-14, -0.4)	
P-value	**0.038**	

Note:
1) Nine subjects (**1031771, 1171054, 1261048, 2071554, 1091800, 2101837, 1211006, 1161770,** and **1031543**) with early effective pain relief before dropout were imputed with LOCF.
2) Adjusted means, confidence intervals, and p-values derived from ANCOVA model with terms for treatment, region, gender, and baseline score as covariate.

Dr. Kim noted in his review that the retrieved drop-out analysis failed to demonstrate a statistically significant difference; however, the difference appeared to favor the nitroglycerin ointment 0.4% treatment group over placebo.

8. Safety

The review of the safety data from Study REC-C-001 did not identify any new adverse event. There were no deaths in the trial, and three serious adverse events reported were reviewed and not felt to be attributable to the product.

The most common adverse events reported were headache, dizziness, diarrhea, and nausea. Among the patients that discontinued secondary to an adverse event, there were more patients in the nitroglycerin treatment group, and the most common reason within that group was "headache." The rest of the safety profile for the product was consistent with the previously reported safety profile for nitrates.

The Applicant submitted a safety update as required in the Completer Response letter. The adverse events reported were consistent with the previously described safety profile.

9. Advisory Committee Meeting

An advisory committee hearing was held on April 26, 2006, during the last review cycle in DCRP. There were no issues identified during this review cycle that required presentation and discussion at an advisory committee meeting.

10. Pediatrics

In the previous submission to this Division, the Applicant had requested a waiver of pediatric studies in patients in the (b) (4) years old age group. The rationale was that pain assessments in that age group would be unreliable, and that the patients would not be able to reliably communicate whether the pain was due to the anal fissure or something else, like a headache. The Applicant proposed to conduct trials in patients (b) (4) years of age, but requested a deferral for this age group at this time. The Applicant's proposal and the Division's assessment of the proposal were not presented to the Pediatric Review Committee (PeRC) during the last review cycle when it became apparent that the application was not going to be approved.

There were no data from pediatric studies included in this submission. The Applicant's proposal in this submission was to ask for a deferral to conduct an open-label safety and efficacy study in patients aged (b) (4) and a waiver from the requirement to study patients (b) (4) of age.

After internal discussions, and in consultation with the PeRC, the review team's conclusion was that the drug development program should include safety and pharmacokinetic studies in pediatric patients in the one month to 17 years age range, with efficacy evaluation to be assessed only in patients three years of age and older; a waiver for patients less than one month

of age was considered acceptable. Specifically, the following five studies are to be requested of the Applicant:

1. A multiple-dose pharmacokinetics study of 0.4% nitroglycerin ointment in pediatric patients ≥ 12 years to < 17 years, in order to determine the appropriate doses for efficacy and safety evaluations.

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

3. A safety, efficacy, and pharmacokinetics study in pediatric patients ≥ 12 years to < 17 years.

4. A safety, efficacy, and pharmacokinetics study in pediatric patients ≥ 3 years to < 12.

5. A safety and pharmacokinetic study in pediatric patients ≥ 1 month to < 3 years.

The purpose of the first study is to characterize the pharmacokinetics of the nitroglycerin ointment after multiple doses, in order to help determine the dose, or doses, which should be utilized in the other two studies. The pharmacokinetic assessments being requested in the second two studies are intended to help determine whether there is any relationship between any adverse events that may be observed and drug exposure; the assessments could be done via sparse blood sampling.

11. Other Relevant Regulatory Issues

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the name Cellegesic and felt that it was unacceptable due to name confusion with "Calagesic" and Alagesic." Several other names were submitted by the Applicant for consideration; the last name submitted, which has been deemed acceptable by DMEPA, was "Rectiv."

There were no new studies conducted to support this submission; therefore, there was no need for the Applicant to include a financial certification or disclosure statement in this submission.

There are no other unresolved relevant regulatory issues.

12. Labeling

The Applicant has submitted adequate information to support their proposed labeling. As noted above, representatives from the Office of Surveillance and Epidemiology and the Division of Drug Marketing, Advertising and Communications were consulted and their recommendations were incorporated during the discussion of the label.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

The Applicant, by utilizing a different imputation strategy than what was utilized in the previous review cycle, has been able to demonstrate a treatment effect for the nitroglycerin ointment. This treatment effect, when taken into account in the context of the safety profile observed, resulted in a favorable risk:benefit assessment.

- Recommendation for Post-marketing Risk Management Activities

None.

- Recommendation for other Post-marketing Study Commitments

The following studies are being requested to satisfy the requirements under the Pediatric Research Equity Act (PREA) of 2003:

1. A multiple-dose pharmacokinetics study of 0.4% nitroglycerin ointment in pediatric patients ≥ 12 years to < 17 years, in order to determine the appropriate doses for efficacy and safety evaluations.

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

3. A safety, efficacy, and pharmacokinetics study in pediatric patients ≥ 12 years to < 17 years. years.

4. A safety, efficacy, and pharmacokinetics study in pediatric patients ≥ 3 years to < 12.

5. A safety and pharmacokinetic study in pediatric patients ≥ 1 month to < 3 years.

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/s/

RIGOBERTO A ROCA
06/21/2011