CLINICAL REVIEW

Application Type	NDA
Submission Number	21-359
Submission Code	N-000 RS
Letter Date	06/30/04
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Reviewer Name	Thomas A. Marciniak, M.D.
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Established Name	nitroglycerin ointment
(Proposed) Trade Name	Cellegesic
Therapeutic Class	vasodilators
Applicant	Cellegy Pharmaceuticals Inc.
Priority Designation	P
Formulation	ointment
Dosing Regimen	375 mg intra-anal every 12 hours
Indication	relief of pain associated with chronic anal fissure
Intended Population	patients with chronic anal fissure

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective I do 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.

1.2 Recommendation on Postmarketing Actions

Because I do not recommend approval of this application, I can not recommend any postmarketing actions.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Cellegesic NTG ointment is a formulation of nitroglycerin (NTG) 0.4% (w/w) in a white petrolatum and lanolin base compatible with a USP monograph. It is intended for use as a self-administered treatment to be applied intra-anally at the site of a chronic anal fissure for relief of pain. The proposed dosing is 375 mg every 12 hours. Because NTG is a drug in widespread us

for many years in approved sublingual and topical formulations, the sponsor did not perform preclinical studies but relied upon literature reports of such studies.

The three clinical efficacy trials reported in the application and mentioned in Section 1.1 were randomized, double-blind, placebo-controlled, parallel group studies. The first study was conducted in the US, while the other two were international studies. All studies enrolled adults with anal fissure, defined as a linear tear of the anoderm distal to the dentate line. Anal fistulas and fissures secondary to recent anal surgery were excluded. For the first study anal pain was not required, but anal pain was mandatory for the second two studies. For the third study a confirmed sentinel pile was also mandatory. While the first study had a primary endpoint of fissure healing at 28 days, average anal pain was recorded daily by the patient on a 100 mm visual analog scale (VAS) in all three studies.

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

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

1.3.2 Efficacy

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

Study NTG 00-02-01 targeted improving the rate of change in daily average pain through 56 days evaluated by a mixed-effects regression model as was done for the first study. By a regression model also incorporating center and quadratic components (not pre-specified and not done for the first study) the sponsor found a significant treatment by linear time interaction for the 0.4% NTG group ($p=0.005$) but not for the 0.2% NTG group. However, besides the issue of lack of pre-specification, the treatment by linear time interaction is not the rate of change.

Evaluating the rate of change by the linear mixed-effects regression model without the center and quadratic components produces statistically insignificant results (p = 0.85 for 0.2% NTG and p = 0.24 for 0.4% NTG).

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

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

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

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

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

1.3.3 Safety

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

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

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

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

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

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

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

1.3.4 Dosing Regimen and Administration

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

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

1.3.5 Drug-Drug Interactions

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

1.3.6 Special Populations

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

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

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Cellegesic NTG ointment is a formulation of nitroglycerin (NTG) 0.4% (w/w) in a white petrolatum and lanolin base. It is intended for use as a self-administered treatment to be applied intra-anally at the site of a chronic anal fissure for relief of pain. The proposed dosing is 375 mg every 12 hours.

2.2 Currently Available Treatment for Indications

There are no approved treatments for anal fissure. Various topical agents (including diltiazem, nifedipine, and corticosteroids) as well as injection of botulinum toxin have been tried, but well-controlled trials documenting their effectiveness have not been done. (Nelson 2003) Accepted conservative treatment for anal fissure is dietary modification, i.e., increased fiber, and stool softeners. For fissures not healing with conservative treatment various surgical procedures have been advocated, with internal lateral sphincterotomy being the standard. (Nelson 2002) Surgery, however, produces fecal incontinence in some patients.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient nitroglycerin has long been available in the U.S. in IV, sublingual, and topical formulations (ointment, patches) for the treatment of angina pectoris.

2.4 Important Issues with Pharmacologically Related Products

Nitroglycerin by sublingual or topical administration has been safely used with recognized adverse effects of hypotension and headaches related to the pharmacodynamic action. With topical use contact dermatitis and fixed drug eruptions have been reported infrequently.

One relevant phenomenon of nitroglycerin use is tolerance. Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of continuously delivered nitrates. In the large majority of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their antianginal efficacy been restored.

2.5 Presubmission Regulatory Activity

The sponsor met with the Division on January 12, 2001, to discuss the disappointing results of the first trial targeting anal fissure healing and problems with recruitment for a second trial targeting pain relief. The Division informed the sponsor that they would need convincing results from the ongoing trial to support approval. The Division and sponsor also discussed that any interim looks at efficacy in the ongoing trial would need to be prespecified and would require adjustment of the p value for the primary analysis.

The sponsor originally submitted an NDA for the use of NTG ointment 0.2% and 0.4% to relieve pain associated with an anal fissure on June 22, 2001. The original NDA contained the results of one pivotal study, NTG 98-02-01. The sponsor amended the application on November 30, 2001, with the results of a second pivotal study, NTG 00-02-01. The Division reviewed this submission. The Division concluded that each of these trials showed a statistical significant benefit of the product only when analyzed by post-hoc analyses, the first study in healing and the second in pain relief. The Division reviewers also questioned whether the marginal benefit of reduced anal pain was offset by the headaches produced by systemic absorption of the NTG. The Division discussed these observations with the sponsor at a teleconference on April 5, 2002. At that teleconference the Division informed the sponsor that a non-approval action was likely and that further clinical studies were needed. The Division also requested that full validation information for an assay used in a pharmacokinetic (PK) study be provided. The sponsor met with the Division on April 22, 2002, and presented its arguments why NTG ointment was effective. The sponsor discussed that NTG was being used in extemporaneous preparations and that the formulation should be uniform and surgery avoided. The Division agreed with these latter statements but maintained that the two trials did not prove efficacy of NTG ointment. The Division Director noted that the application would receive a not approvable action by the April 26, 2002 goal date, unless the sponsor decides to withdraw their application by that date. The Division confirmed at a teleconference on April 24, 2002, that pain would be an acceptable endpoint for another study. The sponsor formally withdrew its application on April 26, 2002.

The Division met with the sponsor again on June 11, 2002, to discuss future development. The sponsor reiterated its belief that the first two trials supported efficacy of the drug and the Division and Office Director disagreed. The Division maintained that the primary analyses need to be pre-specified and that post-hoc adjustments yielding marginal significance were not convincing. The Office Director confirmed that another trial was needed and that it should be long term, although a short term primary endpoint time of 2-3 weeks was acceptable. He also stated that focusing on a subset of patients with anal fissure, such as those with sentinel pile, was acceptable and that standards of care could be specified. The Division Director advised that the sponsor try to establish a clearer temporal relationship between drug use and the frequency and severity of headaches in the next study and suggested using a global pain score.

The sponsor submitted request for a special protocol assessment for a third study on September 16, 2002. The Division's letter dated November 1, 2002, providing the assessment stated that one additional trial convincingly supporting efficacy of the product for pain relief would be sufficient to support approval. The letter advised that restricting standard therapy would not be

acceptable, the specifics of the pain relief question and the timing of the pain evaluated need to be detailed, the timing and relationship of headaches to therapy and timing and use of analgesics should be captured, handling of dropouts should be prespecified to the Division in writing, the details of the proposed complex primary analysis need to be prespecified but that a simple categorical analysis would be preferable and easier to describe in labeling, and the use of diaries is less desirable than a daily evaluation by a blinded assessor.

The sponsor met with the Division on January 31, 2003, to discuss the special protocol assessment. The Division statisticians expressed concern about the sponsor's last observation carried forward (LOCF) approach for handling dropouts and cautioned that a large number of dropouts would make interpretation of the study results impossible. The Division requested that the sponsor submit data on the time course of pain relief with the product prior to starting the trial so that the issue of evaluating the pain at peak (bedtime) could be resolved.

The sponsor submitted revisions to the protocol on February 13 and 27, 2003. The sponsor and the Division had teleconferences on March 20 and April 1, 2003, to discuss the revisions. The relevant issues discussed were the LOCF approach, handling secondary endpoints, and the temporal relationship between product use and pain relief. The Division also sent a letter to the sponsor dated May 16, 2003, explaining the appropriate statistical approaches for controlling alpha for the five secondary endpoints.

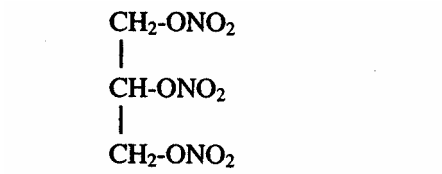
2.6 Other Relevant Background Information

Cellegesic NTG ointment is not currently marketed anywhere. A MAA for Rectogesic NTG ointment 0.4% was submitted to the United Kingdom Committee on Safety of Medicines (CSM) on February 7, 2003. On March 31, 2004, the CSM assessors notified Cellegy UK Ltd that they recommended approval pending responses to some CMC and labeling questions. A NDS for Cellegesic NTG ointment as an over-the-counter product was submitted to the Canadian Therapeutic Products Directorate (CTPD) on March 19, 2002. The CTPD notified Cellegy that the product will be reviewed as a prescription drug. Recently the CTPD sent a notice of deficiency to Cellegy.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The active ingredient is nitroglycerin (1,2,3-propanetriol trinitrate) with the following structural formula:



The ointment is provided in a 0.4% concentrations and is formulated with propylene glycol in a base of lanolin, sorbitan sesquioleate, parafin wax and white petrolatum. A device and a metered dose dispenser are provided to measure out 374 mg of the ointment per dose.

The Division chemistry review dated December 7, 2004, states that the Office of Compliance has not issued a final overall recommendation regarding the cGMP inspections. All other CMC approvability issues have been satisfactorily resolved at this time. This review also notes that a USP monograph is available for NTG ointment. This product is compliant with the monograph.

3.2 Animal Pharmacology/Toxicology

The sponsor did not perform any animal pharmacology or toxicology studies. The NDA provides literature references regarding the preclinical pharmacology and toxicology of NTG, i.e., a 505(b)(2) submission. The Division pharmacology and toxicology reviewer's memo dated August 4, 2004, states that the non-clinical pharmacology and toxicology studies that were included in the June, 2001 original submission were reviewed (Pharmacology/Toxicology Review, 3/14/02). The product was deemed approvable from a non-clinical perspective provided that statements in the sponsor's draft labeling that refer to results of animal toxicity studies be made consistent with labeling used for other nitroglycerin containing products. The resubmission of NDA 21,359 contains no new non-clinical pharmacology and toxicology studies requiring review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source of clinical data for this review was the NDA submission dated June 30, 2004. This submission included paper study reports for all three pivotal studies as well as electronic SAS data sets for them and case report forms (CRFs) in Adobe Acrobat PDF files. In addition, I and other reviewers asked questions to which the sponsor responded with supplemental submissions. The sponsor also submitted additional information regarding extended follow-up and other issues. I've listed all of these submissions in Table 1.

Table 1: NDA 21-359 Submissions Reviewed

Date	Description
June 30, 2004	Primary resubmission
September 21, 2004	Answers to questions regarding randomization

Date	Description
September 30, 2004	Six month follow-up for Study 03-02-01
October 5, 2004	Data submission of corrected CP125 data file
October 22, 2004	Compounding problems with extemporaneous NTG ointment
October 26, 2004	Additional answers on randomization
December 14, 2004	Responses to discipline review letter

4.2 Tables of Clinical Studies

Table 2: Table of Clinical Studies

#	Description	N	Endpoint	Comment
NTG 98-02-02	3-way crossover: 0.2% ointment, IV, placebo	6	PK	50% bioavailable; high variability
NTG 98-02-01	RCT 0.1%, 0.2%, & 0.4% BID or TID (0.75, 1.1., 1.5, 2.3, 3, & 4.5 mg) vs placebo	360	Healing through 56 d	P>.1; pain relief suggested
NTG 00-02-01	RCT 0.2% & 0.4% BID (0.75 & 1.5 mg) vs. placebo	229	Pain through 56 d	Trend significant only with quadratic term
CP125 03-02-01	RCT 0.4% BID (1.5 mg) vs. placebo	193	Pain slope to 21 d	150 planned; 193 analyzed

RCT = randomized controlled trial; PK = pharmacokinetics

4.3 Review Strategy

I depended primarily upon the raw data (SAS data sets and CRFs) for my review with the analysis plans as stated in the protocols. I and the FDA statistical reviewer analyzed the data for the latest study CP125 03-02-01 in depth. I used the Division clinical and statistical reviews from the original NDA submission for the first studies, confirming that I agreed with their analyses. I compared my results to those presented by the sponsor in the study reports and in the sponsor's integrated summary of efficacy (ISE) and integrated summary of safety (ISS).

4.4 Data Quality and Integrity

I recommended sites to be audited from the latest study. I observed that the results at the two sites with the highest enrollments (16 and 20 patients) had among the more favorable results. If these two sites are excluded, then the pain difference between the NTG ointment and placebo groups is virtually nil. The Division of Scientific Investigations (DSI) audited these two sites and judged their data to be acceptable.

Randomization was sloppy as I describe in Section 9.6.1.2.8.1 Number of Subjects, Randomization, and Blinding. The data provided in the SAS data sets corresponded to the

tabulations and analyses in the study report and NDA summaries and in the case report forms (CRFs), although the quality of the copying on some of the CRFs was poor. Copies of the patient diaries were not provided. One limitation of the CRFs is that the amount of information regarding adverse events is very limited.

4.5 Compliance with Good Clinical Practices

I scrutinized only the new submission, CP125 03-02-01. This study was supposed to be conducted following Good Clinical Practices. The protocol was to be reviewed and approved by a local IRB. Each participant was to have provided written consent. Please see the detailed review of this study for comments on two study deviations: (1) The sponsor excluded data from one site in Russia following an unsatisfactory audit. (2) The planned sample size was 150 but 193 subjects were included in the analyses.

4.6 Financial Disclosures

The financial disclosures for NTG 98-02-01 and NTG 98-02-02 were reviewed in association with the original NDA submission and described in a memo filed in DFS dated March 26, 2002. The financial disclosures for these trials as well as NTG 00-02-01 and CP125 03-02-01 are provided in this submission. The sponsor was unable to contact ten investigators for NTG 98-02-01 and NTG 98-02-02 and four investigators for NTG 00-02-01. None of the other investigators had a financial conflict of interest. There is no evidence provided that financial conflicts of interest could have influenced the conduct or outcomes of the trials.

5 CLINICAL PHARMACOLOGY

The sponsor did not provide any new clinical pharmacology studies in this submission. The sponsor provided one pharmacokinetic study, NTG 98-02-02, in the original NDA submission, and the Division biopharmaceutist reviewed it in conjunction with that submission. I summarize the Division biopharmaceutist's review below.

5.1 Pharmacokinetics

The sponsor performed one PK study, NTG 98-02-02, to elucidate the bioavailability and PK of NTG administered intra-anally. The sponsor studied six healthy subjects (four males and two females), ages 25 to 45 years. Five subjects were white and one was Hispanic. The subjects were treated in a random order with single dose intra-anal NTG, repeated dose intra-anal NTG, and IV NTG with seven days washout between phases and dosing as given in Table 3.

Table 3: Treatment phases for PK study

Phase	Concentration	Frequency	Total NTG	Total amount	Route
I	0.2%	qd x1	0.75 mg	~374 mg	Intra-anal
II	0.2%	tid x 7 doses	5.25 mg	~2618 mg	Intra-anal
III	10 µg/mL	1 mL/min constant infusion over 30 minutes	0.3 mg	30 mL	IV

Blood samples for glyceryl trinitrate (NTG) and two principal metabolites, 1, 2-glyceryl dinitrate and 1, 3-glyceryl dinitrate, were collected at the times shown in Table 4.

Table 4: Drug level collection times for PK study

Phase	Blood collection times
I & II	predose, & at 15, 30, 60, 90, 120, 180, 240, 300, 360, and 480 minutes post dose
III	predose, & at 1, 2, 4, 6, 10, 15, 20, 30, 31, 32, 34, 36, 40, 45, 50, 60, 70, 90, 150, 210, and 270 minutes after the start of the infusion

The plasma NTG levels in the study subjects are shown in Figure 1.

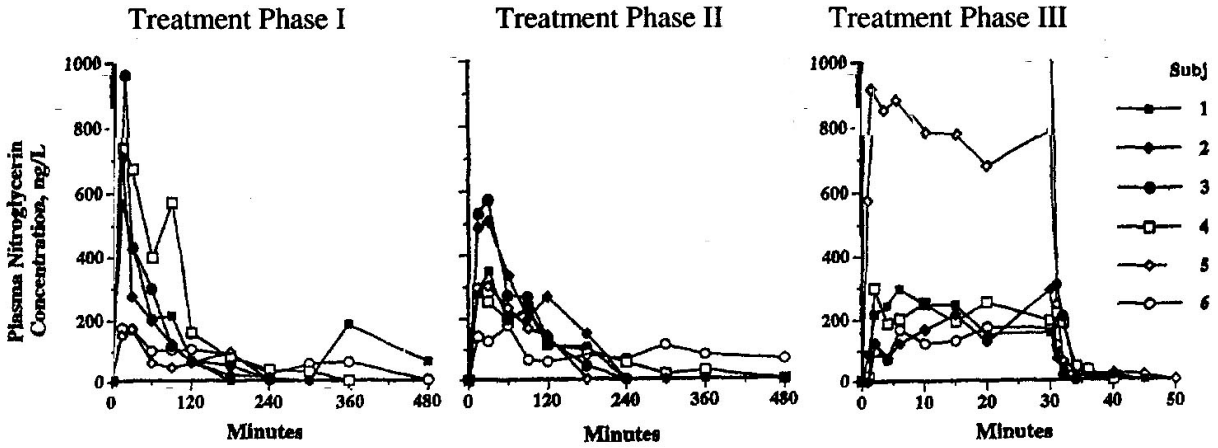


Figure 1: Sponsor's Plasma NTG levels in PK Study

The bioavailability of intra-anal NTG was approximately 50% as shown in Table 5.

Table 5: Sponsor's Bioavailability of Intra-anal NTG in PK study

	Mean Absorption Time (min)		Bioavailability	
	Phase		Phase	
Subject ID	I	II	I	II
1100	192	84	0.77	0.40
1101	56	84	0.47	0.99
1102	53	64	0.20	0.23
1103	79	120	0.77	0.47
1104	98	65	0.084	0.13
1105	167	245	0.49	0.61
Mean (± SD)	108 (± 59)	110 (± 69)	0.46 (± 0.28)	0.47 (± 0.31)

Please see the Division biopharmaceutist's review for other details of the study results, including levels of metabolites.

COMMENT:

- The Division biopharmaceutist reviewer considered the information submitted on the assay used in this study to be inadequate and requested the sponsor to submit full validation information for the assay at a teleconference on April 5, 2002. The current resubmission contains acceptable assay information per the Division biopharmaceutist reviewer's memo dated October 22, 2004.

- Note that this study was performed with the 0.2% formulation rather than the 0.4% formulation now proposed for marketing.

- Table 5 indicates a substantial amount of both inter- and intra-subject variability in the bioavailability of intra-anal NTG. While its effects upon efficacy are difficult to project, it is a safety issue.

- The sponsor also provided a submission dated October 24, 2004, of a report entitled "A Study to Determine Whether Pharmacy Extemporaneous Compounding of Nitroglycerin Ointment Provides a Safe and Effective Treatment of Anal Fissures." This study did not examine safety or efficacy but whether 24 pharmacies compounded 0.3% nitroglycerin ointment appropriately. The report states that 50% of the compounded products did not meet the relevant USP standards for potency and/or content uniformity. About 29% of the compounded products tested did not fall into the range 90-115% of labeled content. This study does not provide data on the safety or efficacy of Cellegesic.

5.2 Pharmacodynamics

Nitroglycerin (NTG) is converted in tissue to nitric oxide. Nitric oxide relaxes smooth muscle, including smooth muscle in arteries and veins. The sponsor proposes that the mechanism of action of NTG ointment is to relax the internal anal sphincter and to increase anoderm blood flow. The sponsor did not provide study reports documenting these actions in this NDA submission but does provide a published reference to a study that used isosorbide dinitrate.

5.3 Exposure-Response Relationships

The sponsor's justification for the proposed dosage and dose schedule is based on its interpretation of the results of the first two pivotal clinical trials. Study NTG 98-02-01 used total daily dosages of 0.75, 1.1., 1.5, 2.3, 3, and 4.5 mg given either BID or TID. The sponsor interprets the results as indicating that pain relief did not differ between those dosed BID or TID (although the primary clinical reviewer of this study expressed concern about lack of sensitivity of the sponsor's ANOVA test supporting this conclusion.) Study NTG 00-02-01 used BID dosing and compared the 0.2% (0.75 mg) and 0.4% (1.5 mg) concentrations. Pain relief was greater with the 0.4% concentration. The primary clinical reviewer found that a greater effect of the 0.4% concentration was evident only for the first week or two. Please see the detailed reviews of the studies in the Appendix.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor's proposed indication is relief of pain associated with chronic anal fissure.

6.1.1 Methods

This submission is a resubmission of an earlier submission that was withdrawn. The earlier submission included the results of two clinical efficacy trials that the Division judged did not provide substantial evidence of efficacy. This submission provides the results of a third clinical efficacy trial. I did not re-analyze the results of the first two trials but used the Division clinical and statistical reviews of them from the earlier submission. I analyzed the data from the third trial and report the details in Section 9.6.1. I summarize my interpretations of all three studies below.

Of the three studies, the latest is the most critical for approval because the Division judged the earlier studies to have nonsignificant results and recommended to the sponsor to perform a third study with convincing results. Also, the first study had a primary endpoint of fissure healing rather than pain relief and all studies had peculiarities in analysis as discussed in the next section.

6.1.2 General Discussion of Endpoints

The primary endpoint for the third study was anal pain relief as evaluated by daily patient diary recordings of average anal pain over the past 24 hours on a 100 mm visual analog scale (VAS). Visual analog scales are commonly used to evaluate subjective entities such as pain. However, the Division advised the sponsor in a pre-study letter that the use of diaries is less desirable than a daily evaluation by a blinded assessor. The Division also expressed concern about evaluating the pain at peak (bedtime). Another concern was that, regardless of whether NTG ointment may relieve anal pain, it causes another type of pain, i.e., headache. The Division suggested to the sponsor to include a global pain assessment at a meeting on June 11, 2002.

Of the two earlier studies, the first had a primary endpoint of anal fissure healing rather than pain relief. The first study failed to demonstrate efficacy of NTG ointment for pain relief. A post hoc analysis suggested a possible benefit of pain relief, so the sponsor performed a second study using anal pain relief (average daily pain evaluated by a 100 mm VAS over 56 days) as the primary endpoint. This second study showed a statistically significant benefit only when analyzed by a quadratic mixed effects model that was not pre-specified. The ambiguities regarding the second study results led to the recommendation to perform a third study. The sponsor decided to perform this third study with the primary endpoint of rate of change of average daily pain over a 21 day period.

COMMENT: Ultimately the Division accepted the sponsor's proposed primary endpoint for the third study in a special protocol assessment.

6.1.3 Study Designs

All three studies were randomized, double-blind, placebo-controlled, parallel group trials. The dosages tested, total enrollments, and endpoints are shown in Table 2. The first study was conducted in the US, while the other two were international studies. All studies enrolled adults with anal fissure, defined as a linear tear of the anoderm distal to the dentate line. Anal fistulas and fissures secondary to recent anal surgery were excluded. For the first study anal pain was not required, but anal pain was mandatory for the second two studies. For the third study a confirmed sentinel pile was also mandatory.

For the first study the primary endpoint was fissure healing at 56 days evaluated by the investigator. To maintain the blind the investigator was not to ask about headache while evaluating fissure healing. In all three studies average anal pain was recorded daily by the patient on a 100 mm VAS. Pain on defecation and worst pain (for the first two studies) were also recorded. For the second study the primary pain relief endpoint was evaluated through 56 days, while for the third study the primary pain endpoint was evaluated through 21 days with a secondary endpoint through 56 days. All three studies attempted to limit use of acetaminophen for headache relief. The first study did not control dietary fiber supplement or sitz bath use, the second specified psyllium 1 tbsp in 8 oz of water BID and limited sitz baths to one per day, and the third allowed continuation of baseline dietary fiber supplements and also limited sitz baths to one per day.

Randomization in all three studies was by computer-generated schedule. In the third study I noted various randomization errors: one site used a higher block prior to using a lower block, another site assigned a block starting with the highest number, and two patients were assigned randomization numbers but never treated.

COMMENT: While all three studies were on paper double-blinded, the occurrence of headache secondary to NTG ointment use introduces the potential for partial unblinding. The use of acetaminophen for headache is a potential confounder of anal pain relief. The randomization errors in the third study suggest some sloppiness in study conduct. All of these factors reduce my confidence in the validity of any positive results. However, as presented below, the results of each of the three studies is negative for other reasons.

6.1.4 Efficacy Findings

6.1.4.1 Study NTG 98-02-01: A Study to Determine the Nitroglycerin Ointment Dose and Dosing Interval That Best Promote the Complete Healing of Chronic Anal Fissures

The primary endpoint for this study was anal fissure healing. The sponsor provided various analyses of anal fissure healing and the FDA statistical reviewer confirmed these results. None

suggested a benefit of NTG ointment to heal the fissures. The results for the analyses pooling the BID and TID dosing groups are shown in Table 6.

Table 6: Sponsor's Study NTG 98-02-01 Anal Fissure Healing Rates

	Healing Rate	
Treatment Group[a]	n (%)	p-value
0.1% NTG (N=76)	30 (40%)	
placebo (N=70)	34 (49%)	p=0.63
0.2% NTG (N=78)	26 (33%)	
placebo (N=70)	34 (49%)	p=0.12
0.4% NTG (N=80)	35 (44%)	
placebo (N=70)	34 (49%)	p=0.64

[a] Results from b.i.d. and t.i.d. dose frequency groups combined.

Pain relief was a secondary endpoint in this study. The sponsor provided a pain analysis pooling the BID and TID dose groups using a mixed effects model. The exact model used and the pooling of the groups were not pre-specified. By this analysis "In the ITT population, linear time by treatment interactions were significant for the 0.4% NTG group relative to placebo for average pain ($p<0.0002$), defecation pain ($p<0.003$) and worst pain ($p<0.0002$). No overall significant differences were observed for the two lower doses relative to the placebo control." These analyses used only 267 of the 304 randomized patients because of missing data. In addition, the FDA reviewers noted imbalances in baseline pain scores among the groups and that the results of the mixed effects model were dependent upon the precise nature of the model used. The FDA statistical reviewer produced the results shown in Table 7 for the mixed effects models.

Table 7: Statistical Reviewer's Study NTG 98-02-01 Slope of Change in Average Daily Pain over Time

	Mean slope (average daily pain)		Nominal P-value*	
	indep	AR(1)	indep	AR(1)
Placebo BID (N=34)	-0.21	-0.21	---	---
0.1% NTG BID (N=39)	-0.23	-0.24	0.86	0.78
0.2% NTG BID (N=39)	-0.27	-0.25	0.62	0.68
0.4% NTG BID (N=38)	-0.52	-0.52	0.005	0.0004
Placebo TID (N=36)	-0.21	-0.19	---	---
0.1% NTG TID (N=37)	-0.37	-0.36	0.12	0.049
0.2% NTG TID (N=39)	-0.32	-0.33	0.27	0.093
0.4% NTG TID (N=42)	-0.37	-0.36	0.14	0.059

* for comparison with the corresponding placebo regimen
Indep: model with independent residuals
AR(1): model with AR(1) residuals

The prior medical reviewer tabulated mean change from baseline to last available daily average pain score in Table 8.

Table 8: Prior Reviewers' Study NTG 98-02-01 Mean Change in Last Available Visit Daily Average Pain from Baseline

	Baseline Mean	Mean change	Nominal p-value[$]	Adj. mean change*	Nominal p-value[#]
0.1% NTG BID	26.4	-9.9	0.85	-12.0	0.46
0.1% NTG TID	35.3	-21.7	0.076	-18.3	0.61
0.2% NTG BID	25.8	-14.9	0.51	-17.4	0.52
0.2% NTG TID	29.9	-23.7	0.031	-23.3	0.059
0.4% NTG BID	39.2	-27.9	0.003	-21.0	0.10
0.4% NTG TID	30.8	-18.9	0.19	-17.9	0.66
Placebo BID	25.7	-11.0	---	-14.9	---
Placebo TID	23.4	-11.6	---	-16.3	---

* adjusted for baseline daily average pain
$ NTG bid vs. placebo bid, NTG tid vs. placebo tid, based on mean change
# NTG bid vs. placebo bid, NTG tid vs. placebo tid, based on adjusted mean change

Please see the combined medical/statistical review of the original NDA submission for more details on this study's results.

COMMENT: This study failed on its primary endpoint, healing of anal fissure. The analyses of pain relief do suggest the possibility that 0.4% NTG ointment may improve anal pain. However, because of the failure of the primary endpoint, the lack of complete pre-specification of the pain analyses, and some inconsistencies in the results (e.g., 0.4% NTG BID appears better than TID but for lower dosages TID is better), the pain analyses of this study must be viewed as exploratory rather than confirmatory.

6.1.4.2 Study NTG 00-02-01: A Study to Determine the Nitroglycerine Ointment Dose that Best Promotes the Relief of Pain Associated with Anal Fissures

The primary endpoint for this study was daily average pain through 56 days evaluated by a mixed-effects regression model using all values recorded for each subject in the ITT population (defined as subjects with baseline and some post-treatment data) The study report states that the effects of center and a quadratic effect of time were included in the model. The center and quadratic components of the model used for analysis were not pre-specified, and these parameters were not used to analyze study NTG 98-02-01. The sponsor concluded that in the ITT population, for comparisons with the placebo group, a significant treatment by linear time interaction for average pain intensity was observed for the 0.4% NTG group (p=0.005), but not for the 0.2% NTG group as shown in Table 9.

Table 9: Sponsor's Primary Endpoint Analysis for Study NTG 00-02-01 (Mixed Effects Regression Model with Center and Quadratic Components)

	Linear trend	p-value for linear*	Quadratic trend	p-value for quadratic*
0.2% NTG minus placebo	-0.055	0.57	0.0013	0.20
0.4% NTG minus placebo	-0.27	0.005	0.0040	< 0.0001

The mixed-effects analysis results depend on the regression model used. Based on the plan of estimating sample size, the model the sponsor intended to use at the time of planning the study was a linear model in which the trend of average pain intensity is linear over time. The previous study NTG98-02-01 also suggested that the linear model was the model to use. In the linear model, the rate of change in pain is the slope of the linear trend that does not change over time. Using the linear model (excluding sites, using a simple covariance matrix for random-effects components and for residual as the sponsor used in Study NTG 98-02-01), the prior reviewer performed the mixed-effects analysis with results summarized in Table 10. Adding sites or using an unstructured covariance matrix for the random-effects components had little impact on the results. Including or excluding the 16 patients who had zero pain at baseline or had no baseline pain data or had no post-randomization pain data recorded made little difference. Based on the linear model, there was no significant difference in slope (rate of change of average pain intensity over time) between either of the NTG groups and the placebo group.

Table 10: Prior Reviewer's Primary Endpoint Analysis for Study NTG 00-02-01 (Slope of Change in Average Daily Pain Over Time Using Linear Model)

	Mean slope	Nominal p-value*
Placebo (N=75)	-0.37	---
0.2% NTG (N=70)	-0.385	0.85
0.4% NTG (N=74)	-0.466	0.24

* for comparison with the placebo group
# the model the sponsor used in Study NTG 98-02-01 (excluding sites, using a simple covariance matrix for random-effects components and for the residual)

The mixed effects regression models are somewhat difficult to visualize. The prior reviewer also performed an analysis of the mean change from baseline to the last available visit of the average daily pain. The results are shown in Table 11. There is little difference among the groups in the mean change in average daily pain at the last available visit.

Table 11: Prior Reviewer's Mean Change from Baseline to Last Available Visit of the Average Daily Pain for Study NTG 00-02-01

	Baseline Mean	Mean change	Nominal p-value[$]	Adj. mean change*	Nominal p-value[#]
0.2% NTG BID	33.8	-18.9	0.78	-19.0	0.73
0.4% NTG BID	34.1	-21.3	0.80	-21.2	0.77
Placebo BID	34.0	-20.2	---	-20.2	---

* adjusted for baseline daily average pain

$ NTG bid vs. placebo bid, based on mean change
# NTG bid vs. placebo bid, based on adjusted mean change

For the secondary efficacy endpoint of anal fissure healing there was no benefit versus placebo noted in either the percentage of patients healed (59% placebo, 59% 0.2% NTG, 54% 0.4% NTG, p = 0.571) or time to healing by Cox regression (p = 0.9984 0.2% NTG, p = 0.7227 0.4% NTG vs placebo).

The prior reviewers also identified problems with missing data. For example, the 0.4% NTG group had a greater percent of the patients who did not complete the pain study compared to placebo (11% for placebo and 24% for 0.4% NTG). Please see the combined medical/statistical review of the original NDA submission for the details on this issue and other results.

COMMENT: The prior reviewer made this cogent comment on these results: While the mixed effects model analyses may suggest a transient difference in the shape of the 0.4% NTG ointment compared to placebo, it is not clear whether this difference would be clinically perceived transiently. At the end of a course of 56 days no difference in pain relief was found. No difference in the number of patients totally relieved of pain was noted. Whatever arguments might be made concerning statistical significance, there do not appear to be meaningful clinical benefits provided.

6.1.4.3 Study CP125 03-02-01: A Study to Determine the Effect of CP125 Ointment on the Pain Associated with a Chronic Anal Fissure

The primary efficacy endpoint for this study was rate of change of the 24-hour average pain intensity over a 21-day treatment period evaluated by a generalized mixed-effects regression model. NTG patients discontinuing the study due to headache were to have their last observation carried forward (LOCF). For this endpoint the sponsor reports a p value of <0.0498 (Table 13 of the study report). The mean changes calculated by the sponsor are -24.9 for placebo and -28.1 for NTG, a difference of 3.2 mm favoring NTG on a 100 mm visual analog scale.

However, the sponsor's handling of some patients' data for its primary analysis is not consistent with the protocol specification. The sponsor did not use LOCF for two patients who discontinued due to headache. For the analysis that matches the description of the primary analysis in the protocol the p value is 0.12. If one argues that post-discontinuation data should be used when available, then the p value is 0.15. For more detail on these analyses see Table 25 and for a complete discussion see the FDA statistical review.

The one secondary efficacy endpoint was the time to 50% improvement in the three-day average (moving window) of 24-hour average pain intensity measurements. By the sponsor's calculation there was no statistically significant difference between the two groups (p<0.3). Fissure healing at 56 days, a tertiary endpoint, was similar in the two groups (placebo 63%, NTG 69%, p = 0.42).

The mean change in pain score from baseline to day 21 was similar in the two groups (placebo -31, NTG -32, see Table 27). Response did not vary significantly by age or gender and race was

predominantly white (95%), making race comparisons impossible. The one subgroup difference I found is that the only country with a substantial improvement in pain scores with NTG is Serbia (see Table 28). US patients fared better with placebo. Serbia had three sites, two of which were among the largest sites and showed substantial improvement with NTG.

COMMENT: By the primary analysis this study fails to show efficacy of NTG ointment for relief of pain with anal fissure. The evidence for efficacy of NTG ointment from this study is even weaker than the p value of 0.12 implies. This study is plagued by a high dropout rate only in the NTG ointment arm: 11 (12%) randomized patients discontinued before day 21, and 9 (9.5%) have incomplete data through day 21 (see Table 20). The Division warned the sponsor that a high dropout rate would make this study uninterpretable. My confidence in any suggestion of a benefit for NTG ointment is weakened further by the potential for partial unblinding because of headaches with NTG ointment and confounding by acetaminophen use and because reasonable improvement with NTG ointment was demonstrated only in one country.

6.1.4.4 Sponsor's Integrated Summary of Efficacy

In its Integrated Summary of Efficacy the sponsor provides two sets of analyses combining data from the three studies: (1) a "combined ITT analysis population" consisting of patients treated with 0.4% NTG ointment or placebo BID (206 placebo and 201 NTG patients); and (2) a "sentinel pile ITT population subgroup" as for (1) but having a sentinel pile, a "well-accepted marker of chronicity" (137 placebo and 118 NTG patients, excluding patients from the first study who did not have sentinel piles recorded). The main results for the combined ITT analysis population are shown in Table 12. The results for the sentinel pile subgroup show similar high statistical significance.

Table 12: Sponsor's Change from Baseline in 21- and 56-Day Measurements of 24-Hour Average Pain Intensity (mm) – Combined Analysis

Time Period	Statistics[a]	Placebo (N=206)	Cellegesic Nitroglycerin Ointment 0.4% (N=201)	P-value[b]
Baseline	N	204	198	N/A
	Mean (SD)	42.3 (22.53)	44.2 (22.38)	
	Median	44.0	44.0	
	Min, Max	0.0, 98.0	1.0, 100.0	
Days 1-21	N	203	194	<0.0007
	Mean (SD)	-15.4 (19.33)	-19.3 (20.53)	
	Median	-12.7	-17.7	
	Min, Max	-77.0, 24.0	-76.6, 63.5	
Days 1-56	N	203	194	<0.0001
	Mean (SD)	-22.4 (20.80)	-25.8 (21.96)	
	Median	-22.9	-27.9	
	Min, Max	-88.2, 20.2	-75.8, 57.3	

Combined analysis includes all ITT subjects who applied Cellegesic NTG ointment 0.4% b.i.d. or placebo b.i.d. in studies NTG 98-02-01, NTG 00-02-01, and CP125 03-02-01.
[a] Summary statistics displayed at the above intervals are calculated by using the mean of daily change from baseline in 24-hour average pain intensity assessments recorded for each subject during the indicated interval.
[b] Analysis of the raw daily pain intensity assessments from Baseline through Day 21 or 56 used a mixed-effects regression model. The P-values are from the test of the linear component of the treatment-by-day interaction (i.e., the rate of change in pain is different between placebo and Cellegesic-treated subjects).

Note: The N's in the column headers are the number of subjects in the ITT population.
The N's in the time period rows are the number of ITT subjects having data for the descriptive statistics for that time period.

COMMENT: The fundamental problem with these analyses is that they were not pre-specified. They are subject to unstated selection criteria that may be used to produce positive results and misleadingly low p values. The Division statistical reviewer shows in his review the great variations in p values resulting from inclusion or exclusion of a few data values in the analyses of the most recent study. The prior reviewers have discussed in their review the variations in p values resulting from variations in how the mixed effects regression model is run for the second study. The variability of the results is also demonstrated by examining the results for the patients that the sponsor excluded from these analyses, i.e., the patients treated with 0.2% NTG ointment. One would like to see a dose response relationship to confirm that NTG is showing an effect rather than a chance outcome. I show in Table 13 the mean change from baseline to day 21 in pain score for BID dosing in all three studies, including the 0.2% NTG patients.

Table 13: Reviewer's Mean Change from Baseline to Day 21 in Pain Score for BID Dosing in All Three Studies

Dose	N	Mean	SD
Placebo	203	-20.4	23.1
0.2	97	-13.5	25.6
0.4	189	-26.1	25.8

Note that there is no suggestion of a dose response for NTG ointment—0.2% NTG appears as worse than placebo as 0.4% appears better. I also note that the absolute differences in the pain

scores are small, e.g., < 6 mm or < 6% for 0.4% NTG vs. placebo, compared to the variability (SD about 25 mm). These studies, whether analyzed individually or collectively, provide little suggestion and no substantial evidence that NTG ointment relieves the pain of anal fissure.

6.1.5 Clinical Microbiology

This section is not applicable because this drug is not an antimicrobial.

6.1.6 Efficacy Conclusions

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

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

For the evaluation of safety issues related specifically to NTG ointment I relied upon the data and tabulations provided in this submission for the four studies identified in Table 2. For safety issues related to systemic absorption of NTG I used the safety information in the approved labeling for other NTG formulations.

7.1.1 Deaths

No deaths occurred during the clinical trials.

7.1.2 Other Serious Adverse Events

Ten patients experienced serious adverse events (SAEs) during the trials, four placebo, two 0.4% NTG BID, and four other NTG dosing. The SAEs are listed in Table 14.

Table 14: Sponsor's Serious Adverse Events

Treatment Group Study Number Subject Number	Age (Yrs)	Serious Adverse Event (Preferred Term)	D/C Study Drug[a]	Study Day of Onset[b]	Intensity	Relationship to Study Drug[c]	Duration of Event (Days)
Placebo ointment b.i.d.							
NTG 00-02-01							
007-123	19	Pain exacerbated	Yes	22	Moderate	None	22
015-106	46	Hepatitis C	No	3	Moderate	None	Ongoing
CP125 03-02-01							
025-109	52	Vein pain	No	1	Moderate	None	5
033-340	41	Perianal abscess	No	60	Moderate	None	14
Cellegesic nitroglycerin ointment (0.1%) t.i.d.							
NTG 98-02-01							
312-113[d]	42	Cholelithiasis	No	23	Moderate	None	23
Cellegesic nitroglycerin ointment (0.2%) b.i.d.							
NTG 98-02-01							
322-146[d]	24	Perirectal abscess	Yes	8	Severe	None	2
NTG 00-02-01							
009-110	41	Migraine NOS	Yes	1	Severe	Related	1
Cellegesic nitroglycerin ointment (0.2%) t.i.d.							
NTG 98-02-01							
320-103[d]	63	Chest pain	No	34	Severe	None	3
		Dyspnea NOS	No	34	Severe	None	3
Cellegesic nitroglycerin ointment (0.4%) b.i.d.							
NTG 98-02-01							
317-115[e]	72	Hip fracture	Yes	48	Severe	None	1
CP125 03-02-01							
019-045	69	Abdominal distension	No	50	Mild	None	42
		Abdominal pain NOS	No	46	Severe	None	46
		Anorexia	No	50	Moderate	None	42
		Dyspnea NOS	No	51	Moderate	None	39
		Dysuria	No	50	Mild	None	Ongoing
		Hemoglobin decreased	No	53	Moderate	None	25
		Hypercalcaemia	No	53	Severe	None	Ongoing
		Loose stools	No	47	Moderate	None	Ongoing
		Nausea	No	52	Moderate	None	33
		Night sweats	No	50	Mild	None	2
		Pyrexia	No	48	Mild	None	44
		Rigors	No	50	Mild	None	3
		Small intestinal obstruction NOS	No	50	Severe	None	42
		Weakness	No	50	Moderate	None	Ongoing

[a] Subject discontinued therapy due to this adverse event.
[b] Relative to start of therapy.
[c] Based on investigator's assessment.
[d] For these 3 subjects, the duration of event was reported incorrectly in Table 19 Subjects with Serious Adverse Events in Report NTG 98-03-01, 8;v05;p079 For Subject 312-113 (duration 23 days) and Subject 322-146(duration 2 days), durations of event were reported as 1 day. For Subject 320-103 (duration 3 days), duration was reported as 2 days.
[e] For Subject 317-115, onset of event (Day 48) was reported as Day 47 in Table 19 Subjects with Serious Adverse Events in Report NTG 98-03-01, 8;v05;p079 .

The patient with the chest pain and dyspnea SAE was a 63 year-old white male with a history of coronary artery disease, hypertension, and angioplasty. He was hospitalized on day 37 with chest pain and dyspnea, underwent catheterization and angioplasty, and was discharged after three days. He subsequently completed the study.

COMMENT: The SAEs were infrequent, uncorrelated, and not suggestive of any unusual problem with anal administration of NTG.

7.1.3 Dropouts and Other Significant Adverse Events

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

One AE in a 0.4% BID patient was coded as syncope but the CRF records "faintness following cream application" of mild intensity lasting several days. Another 0.4% BID patient had nausea, vomiting, and vertigo leading to moderate tachycardia and discontinuation. A 0.2% BID patient had moderation dizziness, faintness, and palpitations and another one had worsening vertigo of moderate intensity. A 0.2% TID patient also had moderate vertigo along with headache. Other details and blood pressure measurements are not available for these patients.

COMMENT: The withdrawal AEs confirm that the systemic absorption of NTG from the ointment can cause systemic effects. The headaches may not be dangerous, but they do confound the interpretation of the pain scores. Was anal pain rated less intense because the patient was more concerned with the headache? This problem was the reason why the Division recommended to the sponsor to capture a global assessment of pain, but the sponsor ignored this suggestion. The dizziness and faintness suggest that the systemic absorption of NTG may also be causing hypotension. Whether this AE could lead to more serious problems in more vulnerable patients or those taking other medications is not determinable from this small safety data base.

7.1.4 Other Search Strategies

For this small safety data base no other search strategies were employed or are needed.

7.1.5 Common Adverse Events

The AES occurring at a frequency =2% in any treatment group are shown in Table 15. Severe headaches were reported in about 20% of NTG 0.4% BID patients but only 6% of placebo patients.

COMMENT: Note the higher rate of headaches, dizziness, and nausea in the NTG patients.

Table 15: Sponsor's Adverse Events =2% Frequency in Any Treatment Group

		Cellegesic Nitroglycerin Ointment	
	Placebo[a] (N=246)	0.4% b.i.d. (N=206)	Total[b] (N=475)
Body System Preferred Term	n (%)	n (%)	n (%)
Subjects With Any Adverse Events	149 (60.6)	162 (78.6)	315 (66.3)
Nervous system disorders	95 (38.6)	138 (67.0)	243 (51.2)
Headache NOS	93 (37.8)	131 (63.6)	229 (48.2)
Dizziness	0	9 (4.4)	17 (3.6)
Gastrointestinal disorders	39 (15.9)	36 (17.5)	78 (16.4)
Nausea	2 (0.8)	12 (5.8)	21 (4.4)
Diarrhea NOS	8 (3.3)	6 (2.9)	12 (2.5)
Hemorrhoids	0	5 (2.4)	6 (1.3)
Anal discomfort	6 (2.4)	1 (0.5)	1 (0.2)
Infections and infestations	31 (12.6)	17 (8.3)	36 (7.6)
Upper respiratory tract infection NOS	7 (2.8)	2 (1.0)	6 (1.3)
Influenza	6 (2.4)	1 (0.5)	4 (0.8)
Respiratory, thoracic and mediastinal disorders	13 (5.3)	9 (4.4)	21 (4.4)
Pharyngitis	5 (2.0)	2 (1.0)	6 (1.3)
Skin and subcutaneous tissue disorders	10 (4.1)	6 (2.9)	9 (1.9)
Pruritus NOS	6 (2.4)	1 (0.5)	1 (0.2)

[a] Includes all subjects receiving placebo (b.i.d. or t.i.d.).
[b] Includes all subjects receiving any concentration of Cellegesic ointment (0.1%, 0.2%, or 0.4%) b.i.d. or t.i.d.

7.1.6 Less Common Adverse Events

The safety database is too small to evaluate less common AEs.

7.1.7 Laboratory Findings

Routine safety labs (hematology, clinical chemistry, and urinalysis) were measured at baseline and at day 56 or study exit. Shifts from normal at baseline to abnormal at day 56 were infrequent and similar between placebo and NTG patients. The most frequent abnormality was a high blood glucose (12-15% of all patients at day 56 in all groups), but samples were not necessarily collected fasting. There were also similar frequencies of increased creatinines (6-7%) and increased SGOT or SGPT (3-6%). Follow-up on abnormalities judged clinically significant did not document any abnormalities clearly related to study drug.

COMMENT: NTG use sublingually or topically has not been associated with laboratory abnormalities other than methemoglobinemia with overdose.

7.1.8 Vital Signs

Vital signs were measured at baseline (prior to the first study drug use) and post-baseline at days 1 (10-20 minutes post-dose for this visit only), 14, 28, 42, and exit visits in studies NTG 98-02-01 and NTG 00-02-01 and at the day 7, 21, 35, and exit visits in study CP125 03-02-01. The NDA comments that there were no time- or dose-related trends in DBP, SBP, or pulse. The sponsor also examined decreases in DBP of =20 mm Hg as shown in Table 16.

Table 16: Sponsor's Decreases in Sitting DBP of =20 mm Hg

		Cellegesic Nitroglycerin Ointment				
				0.4%		
Visit[a]	Placebo[b] n/N (%)	0.1%[b] n/N (%)	0.2%[b] n/N (%)	b.i.d. n/N (%)	Total[c] n/N (%)	Total[d] n/N (%)
Day 1	2/147 (1.4)	5/ 74 (6.8)	2/151 (1.3)	7/115 (6.1)	9/157 (5.7)	16/382 (4.2)
Day 7-14	10/237 (4.2)	5/ 65 (7.7)	5/136 (3.7)	5/184 (2.7)	9/219 (4.1)	19/420 (4.5)
Day 21-28	12/226 (5.3)	6/ 60 (10.0)	7/123 (5.7)	8/178 (4.5)	11/208 (5.3)	24/391 (6.1)
Day 35-42	7/211 (3.3)	6/ 41 (14.6)	6/107 (5.6)	3/165 (1.8)	6/190 (3.2)	18/338 (5.3)
Exit	9/227 (4.0)	5/ 64 (7.8)	2/131 (1.5)	9/187 (4.8)	11/225 (4.9)	18/420 (4.3)
Any Post-baseline	24/246 (9.8)	13/ 76 (17.1)	10/151 (6.6)	21/203 (10.3)	30/245 (12.2)	53/472 (11.2)

[a] Baseline is the last measurement taken prior to the first CTM application. Post-baseline vital signs were to be collected at the Day 1 (10-20 minutes post-dose), 14, 28, 42, and exit visits in Studies NTG 98-02-01 and NTG 00-02-01, and at the Day 7, 21, 35, and exit visits in study CP125 03-02-01.
[b] Includes all subjects receiving the indicated treatment (b.i.d. or t.i.d.).
[c] Includes all subjects receiving any Cellegesic 0.4% (b.i.d. or t.i.d.).
[d] Includes all subjects receiving any concentration of Cellegesic (0.1%, 0.2%, or 0.4%) b.i.d. or t.i.d.
NOTE: n = number of subjects with a decrease from baseline at the indicated visit
N = number of subjects with a diastolic blood pressure at baseline and the indicated visit.

COMMENT: Because vital sign measurements were not timed for peak drug effect after the first visit, most of the measurements are not helpful.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were recorded only in study CP125 03-02-01. One NTG patient withdrew because of bradycardia and extrasystoles, the only abnormality considered "clinically significant". Between 72 and 82% of ECGs were considered normal at any time, and the rates of "not clinically significant" abnormalities in both groups decreased slightly from screening to last visit.

COMMENT: ECGs were only evaluated qualitatively and QTc and other interval measurements at peak drug effect were not done. Given the vast experience with oral and topical NTG, a thorough QTc study is not needed.

7.1.10 Immunogenicity

Immunogenicity was not evaluated.

COMMENT: Topical NTG use has been associated with contact dermatitis or fixed drug eruptions. The safety database is too small to rule out rare problems with anal NTG administration.

7.1.11 Human Carcinogenicity

The safety database is too small and of limited duration to provide any information regarding human carcinogenicity.

7.1.12 Special Safety Studies

No special safety studies were done.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No withdrawal studies were done.

COMMENT: Rebound hypertension has been reported with withdrawal of NTG. Given the unpleasant adverse effect (headache), the abuse potential is low.

7.1.14 Human Reproduction and Pregnancy Data

There have been no clinical studies of the effects of NTG in pregnant women.

7.1.15 Assessment of Effect on Growth

Only adult patients were studied.

7.1.16 Overdose Experience

There were no overdoses in the clinical studies.

7.1.17 Postmarketing Experience

Cellegesic has not been marketed anywhere.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The three randomized, placebo-controlled trials and the one small pharmacokinetic study that provide the safety data for this NDA are identified in Table 2. Of the 726 patients enrolled in the three trials, 475 received any dose of NTG (0.1%, 0.2%, or 0.4%) BID or TID and 206 patients received 0.4% BID, the regimen proposed to be marketed. Of these 206, 167 (81%) completed a 56-day treatment period. The most frequent reason for withdrawal was adverse event in 20 (10%), but another 13 (6%) withdrew for "patient choice".

7.2.1.2 Demographics

The demographics of the safety population are shown in Table 17.

Table 17: Sponsor's Demographics of Safety Population

		Cellegesic Nitroglycerin Ointment		
	Placebo[a] (N=246) n (%)	0.4% b.i.d. (N=206) n (%)	Total[b] (N=475) n (%)	Overall Total (N=721) n (%)
Sex				
Male	119 (48.4)	90 (43.7)	246 (51.8)	365 (50.6)
Female	127 (51.6)	116 (56.3)	229 (48.2)	356 (49.4)
Race				
Caucasian	219 (89.0)	187 (90.8)	408 (85.9)	627 (87.0)
Black	13 (5.3)	8 (3.9)	29 (6.1)	42 (5.8)
Asian	5 (2.0)	1 (0.5)	4 (0.8)	9 (1.2)
Hispanic/American or Latino	8 (3.3)	9 (4.4)	26 (5.5)	34 (4.7)
Native American	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Other	1 (0.4)	1 (0.5)	7 (1.5)	8 (1.1)
Age (years)				
≤45	128 (52.0)	99 (48.1)	264 (55.6)	392 (54.4)
46-64	96 (39.0)	87 (42.2)	173 (36.4)	269 (37.3)
65-74	17 (6.9)	17 (8.3)	30 (6.3)	47 (6.5)
≥75	5 (2.0)	2 (1.0)	7 (1.5)	12 (1.7)
N	246	205	474	720
Mean±SD	45.2±13.01	46.2±12.95	44.3±13.09	44.6±13.06
Range	19.0-81.0	19.0-76.0	19.0-83.0	19.0-83.0
Missing	0	1	1	1

COMMENT: Note that the safety population has a reasonable gender split but is predominantly white (90%) and middle aged (mean 46). The one subgroup representation for which more exposure would be desirable is the elderly, because they have a higher rates of chronic cardiovascular disease for which adverse effects such as hypotension would be more

troublesome. Only 19 patients 65 or older were exposed to the regimen proposed to be marketed. However, given the widespread use of sublingual and topical NTG, the extent of safety exposure to anal NTG is not critical.

7.2.1.3 Extent of exposure (dose/duration)

The extent of exposure is shown in Table 18.

Table 18: Sponsor's Extent of Exposure

		Cellegesic Nitroglycerin Ointment	
	Placebo (N=246) n (%)	0.4% b.i.d. (N=206) n (%)	Total (N=475) n (%)
Duration of Therapy (days)			
1-7	1 (0.4)	9 (4.4)	18 (3.8)
8-21	11 (4.5)	8 (3.9)	28 (5.9)
22-35	8 (3.3)	12 (5.8)	42 (8.8)
36-56	95 (38.6)	85 (41.3)	138 (29.1)
>56	109 (44.3)	76 (36.9)	195 (41.1)
Missing	22 (8.9)	16 (7.8)	54 (11.4)
Total Amount of CTM Administered (grams)			
N	224	188	419
Mean±SD	42.6±15.20	39.8±17.65	38.7±19.04
Range	1.5-86.9	0.4-83.8	0.4-102.1
Missing	22	18	56
Percent compliance			
N	223	187	418
Mean±SD	101.2±31.60	104.9±36.26	94.3±35.28
Range	24.1-254.6	1.3-244.4	1.3-252.8

COMMENT: The extent of exposure in terms of patient exposure years is low (about 28). The safety evaluation of this drug depends upon the vast experience with NTG by sublingual and topical administration. However, some potential problems of this new preparation, e.g., variable systemic absorption by the anal route, can not be addressed by the sublingual and topical administration experiences.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

I also used the descriptions of adverse events included in the approved labels for sublingual and topical NTG.

7.2.2.1 Other studies

In addition to the three clinical efficacy trials the safety data from one small pharmacokinetic study in healthy volunteers is provided.

7.2.2.2 Postmarketing experience

Cellegesic has not been marketed anywhere.

7.2.2.3 Literature

The sponsor provided a summary of uncontrolled and controlled studies of anal application of medications containing a nitric oxide donor. The published studies reported AEs similar to those in the NDA studies, e.g., headache was the most frequent AE. No unusual toxicities were reported.

7.2.3 Adequacy of Overall Clinical Experience

For NTG ointment 475 patients were exposed to some dosage, 206 started the regimen proposed to be marketed (0.4% BID), 167 completed a 56-day treatment period with this regimen, and only 19 patients of the latter patients were age 65 or older. This is fairly limited exposure for a new route of administration. I am most concerned about exposures for vulnerable patients with other cardiovascular diseases.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal studies were submitted or are needed for NTG.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing had two limitations:

- Vital signs were not obtained at the time of estimated peak drug levels after chronic exposure. It would be helpful to know how much blood pressure is affected and the variability of it.

- The case report forms provided minimal information on the adverse events. For example, tachycardia was reported for several patients but no information is provided on heart rate, heart rhythm, or blood pressure.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Because NTG has had widespread clinical use, no workup was done for metabolism, clearance, or drug interaction and none is indicated.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The potential for cardiovascular AEs in individuals with existing cardiovascular disease has not been adequately evaluated and should be studied further. The effects of intra-anal administration on heart rate and blood pressure are not documented adequately and should be studied further.

7.2.8 Assessment of Quality and Completeness of Data

Please see the two comments in Section 7.2.5.

7.2.9 Additional Submissions, Including Safety Update

The sponsor provided a submission dated September 30, 2004, with the first six-month follow-up data from study CP125 03-02-01. Data were provided for 175 subjects (89 placebo and 86 NTG). This supplement provided information on subsequent treatments rather than safety data.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

NTG administered intra-anally is systemically absorbed—bioavailability about 50% with a wide SD of about ± 30%. Not surprisingly, NTG ointment causes AEs typical of systemic administration of NTG such as headaches. While the headaches may be considered more of a nuisance AE, other effects of systemic administration of NTG, such as hypotension, may be troublesome in patients with existing cardiovascular disease. The potential or lack of potential of NTG ointment for causing dangerous cardiovascular AEs is not well explored in the limited exposure in the Cellegesic development program with limited information on blood pressure changes and AEs. While the available data don't confirm that NTG ointment is a dangerous drug, they also don't provide sufficient reassurance that it is safe.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The sponsor pooled data for the regimen proposed to be marketed (0.4% BID) and for all NTG ointment use as well as presented the individual regimen's data. The sponsor also reported each study's data individually. All of these analyses are appropriate.

COMMENT: Despite the pooling the size of the safety database is small.

7.4.2 Explorations for Predictive Factors

The size of the safety database is too small to facilitate exploration for predictive factors.

7.4.3 Causality Determination

The most frequent AE, headache, is a recognized side effect of systemic NTG exposure.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing regimen was selected based on the first study examining a range of doses (0.1, 0.2, and 0.4%) and BID and TID dosing and the second study testing 0.2 and 0.4% BID. The regimen selected for the third study and proposed to be marketed was selected based on the suggestion of best pain relief and a rate of adverse effects (i.e., headache) considered tolerable. The evidence for efficacy of the 0.4% BID regimen was weak and not supported by the third study. The rate of headaches with the 0.4% BID regimen suggests that higher doses would not be acceptable.

The sponsor proposes marketing CELLEGESIC nitroglycerin ointment 0.4% in both a metered dose canister and in a tube. The canister has a metered dose-dispensing pump that delivers approximately 375 mg ointment each time the piston is fully depressed. To obtain a 375 mg dose of ointment with the tube, a finger cot or plastic food wrapped finger is laid alongside the dosing line on the carton. The tube is gently squeezed until a ribbon of ointment the length of the line is expressed onto the covered finger. Once the dose is dispensed the finger is gently inserted into the anal canal to the first knuckle (joint) to apply the ointment around the side of the anal canal.

The 375 mg dose of 0.4% NTG ointment contains about 1.5 mg of NTG. The bioavailability of NTG from the NTG ointment varied widely even in the small pharmacokinetic study in normal volunteers (e.g., range 8% to 99% intersubject and as high as 40% to 77% intrasubject, with a mean absorption time of about 110 minutes and a range of 53 to 245 minutes--see Table 5.) For average bioavailability numbers the 375 mg dose of 0.4% NTG ointment delivers about 0.4 mg/hour, comparable to rates of systemic NTG delivery from NTG patches for angina. For the highest extremes of bioavailability the proposed dose delivers about 1.7 mg in the first hour, substantially higher than the usual antianginal dosages.

COMMENT: I believe that the failure of this development program lies not with an inappropriate regimen but with inadequate efficacy of NTG for this condition. The 0.4% BID regiment has been tested in three studies, produces a substantial rate of severe headaches, and has consistently failed to show substantial efficacy.

The estimates on the variability of NTG systemic variability above are likely low. As can be judged from the description of the dispensing, patients are likely to administer higher or lower doses than prescribed because of measuring error. In the two sites that were audited the DSI inspector found substantial overdosage by patients, as high as fourfold. I am concerned that a delivery rate of 1.7 mg or higher in the first hour could be dangerous in vulnerable patients and that the size of the safety database is too small to exclude such problems.

8.2 Drug-Drug Interactions

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

8.3 Special Populations

The sponsor did not study any special populations except both genders were adequately represented in the clinical trials. Blacks and the elderly are sparsely represented in the clinical studies (see Table 17).

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

8.4 Pediatrics

The Division granted a deferral of pediatric studies in a letter dated August 26, 2004, because the drug would be ready for approval in adults before studies in children would be completed. The Division also requested that the sponsor submit a general plan and timeline for their pediatric development program by December 27, 2004

8.5 Advisory Committee Meeting

This NDA has not been and is not planned to be discussed at an advisory committee meeting.

8.6 Literature Review

The sponsor provided a literature review of NTG and related nitric oxide donors used for the treatment of anal fissure. I searched Medline for references regarding NTG ointment use for treating anal fissure. In addition to references cited in the NDA expressing positive results for NTG ointment I found the following references raising questions about the efficacy of NTG ointment in anal fissure:

- A prospective, double-blind study published in 2004 randomized 48 patients to placebo, 0.2%, or 0.4% NTG ointment. (Weinstein, Halevy et al. 2004) The study found no benefit regarding healing or pain relief in treating patients suffering from an anal fissure with

NTG ointment in combination with stool softeners and sitz baths, compared to the same treatment without NTG ointment.

- A Cochrane review examined non-surgical therapy for anal fissure. (Nelson 2003) Excluding two studies with quality concerns, NTG ointment was not significantly better than placebo in curing anal fissure. This meta-analysis did not address pain relief.

8.7 Postmarketing Risk Management Plan

The sponsor did not propose a postmarketing risk management plan.

8.8 Other Relevant Materials

There are no other relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

All three of the major clinical studies submitted to support this NDA fail to show a statistically significant and clinically meaningful benefit of NTG ointment in the relief of pain associated with chronic anal fissure. The first study, NTG 98-02-01, failed for its primary endpoint of fissure healing, but the sponsor interpreted some secondary analyses as suggesting a beneficial effect upon pain. The second study, NTG 00-02-01, showed a statistically significant result only when analyzed with a quadratic term included in the mixed effects regression model that was not specified in the protocol. Using a linear model the p value is 0.24 for 0.4% NTG ointment. The third study, CP125 03-02-01, showed a statistically significant effect ($p < 0.0498$) in a sponsor's analysis selectively apply last observation carried forward (LOCF) to some NTG patients discontinuing for headache. When LOCF is applied to all NTG patients discontinuing for headache as specified in the protocol, the p value is 0.12.

Study CP125 03-02-01 also has other weaknesses. The estimated magnitude of a benefit, if any, of NTG in relieving pain of anal fissure is small, e.g., a mean improvement of about 3 mm on a 100 mm visual analog scale even with the sponsor's liberal analysis. Other problems are excessive dropouts with NTG, greater acetaminophen use for headache in the NTG group, and benefit limited to one country.

These studies do not provide substantial evidence of efficacy of NTG ointment in relief of pain associated with chronic anal fissure.

The data supporting safety are also weak. The numbers of patients initially exposed (206) and completing (167) a typical treatment period with the regimen proposed to be marketed are low.

Only 19 of the latter patients were age 65 or older. The monitoring in the clinical trials also had some weaknesses: Vital signs were not obtained at the time of estimated peak drug levels after chronic exposure so that effects upon blood pressure are known. The case report forms provided minimal information on the adverse events so that the severity and criticality of some events, e.g., tachycardia, is difficult to assess.

The Division sent the sponsor a discipline review letter dated December 10, 2004, summarizing the critical issues regarding efficacy and safety. The critical issues were the following, and I have summarized the sponsor's responses to them dated December 14, 2004, and my comments on the responses:

1. *The protocol says that imputation would be applied to subjects who withdrew for reasons of headache, but in the analysis of study 03-02-01, imputation was restricted to subjects whose headaches were attributed to study drug. How is this justified?*

The sponsor quotes the protocol section regarding AEs, which does specify a criterion that only headaches occurring within 30 minutes of NTG administration will be considered a NTG-related AE, and the protocol section on the primary analysis, which does not impose such a restriction. We consistently maintain that attributions of causality, such as the 30-minute limit, are futile and that the more appropriate approach is to include all headaches for the LOCF analyses. We believe that the protocol and our discussions with the sponsor are consistent with that position.

2. *Four subjects randomized to nitroglycerin ointment (NTG) in study 03–02–01 have no data post randomization. Seven more NTG subjects discontinued prior to 21 days. No placebo subjects did. What are the implications on the interpretability of the findings of study 03-02-01 of having the observed imbalance between groups in the number of subjects withdrawn in the first 21 days*?

The sponsor responded that the assertion that four subjects randomized to NTG have no data is not correct. The sponsor is neglecting to count the two subjects that were assigned randomization numbers but allegedly failed to start treatment. These subjects were identified by the sponsor in an earlier response and are accounted for in Table 20.

The sponsor goes on to claim that the generalized mixed-effects regression model supports validity regardless of missing data. The sponsor ignores the possibility that "The assumption of the model is that the data that are available for a given subject are representative of that subject's deviation from the average trend lines that are observed for the whole sample" is not true. The latter is an assumption, not a fact.

3. *What is the plausible clinical significance of a 3-mm mean difference in the anal pain visual analog scale, when this magnitude of effect is 13% of the placebo effect, and how does this difference balance against a high rate of withdrawal for headache and other adverse events*?

The sponsor responded that the agreement from the special protocol assessment was for a primary endpoint for rate of change, not for the mean difference. The sponsor does not consider

that this rate of change was not significant if the pre-specified analysis is followed. The sponsor also does not consider that confidence in this small effect is weakened by the withdrawals (as the Division warned the sponsor during discussions) and must be weighed in a risk-benefit analysis against the adverse effects. The sponsor also does not consider that the Division advised that the third study would have to show substantial benefit if it was to stand alone as a single significant study. The sponsor in its response does quote its selective analyses of data from the three studies, but these analyses are "not part of the agreed upon analyses" (i.e., not pre-specified.)

4. *In study 03-02-01 one NTG patient withdrew because of dizziness, bradycardia, and extrasystoles and another withdrew because of tachycardia, both adverse events suggestive of systemic cardiovascular effects of NTG absorption. Your pharmacokinetic study documented about 50% bioavailability of NTG with wide variability (± 30%). How well does your clinical safety database characterize the variability in systemic cardiovascular effects of NTG ointment, e.g., time course of vital signs post administration in patients and during adverse events? How much assurance does your clinical safety database provide of cardiovascular safety, particularly for patients with underlying cardiovascular disease? How do these potentially serious adverse effects balance against a minimal symptomatic benefit?*

The sponsor expresses dismay in its opening remarks that the Division is considering safety. Apparently the sponsor believes that filing as a 505(b)(2) transfers the burden of establishing safety to the Division: "Our NDA was filed as a 505 (b)(2) which we understand relies upon existing safety information, much of which is in the form of a very large database available to the Agency for NTG." Regarding the two patients withdrawing because of possible cardiovascular events the sponsor qualifies the first as "moderate" bradycardia and second as no explanation for the recording of tachycardia. This lack of information about potentially serious adverse events remains disturbing. The sponsor provides estimates of plasma NTG levels that ignore the variability shown both in its PK study and in the clinical trials.

5. *Only 19 patients aged 65 or older completed treatment with 0.4% NTG BID in your studies. Your proposed label suggests that 'Clinical data from the published literature indicate that the elderly demonstrate increased sensitivity to nitrates, which may reflect the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.' How does the exposure in your studies support safe administration in the elderly?*

The sponsor admitted that only 19 patients aged 65 or older completed treatment with 0.4% NTG BID. Its response is that "There are ample data available to the Agency on the safety of NTG in the elderly and other special populations." This response ignores the problem that the variability in systemic availability from their product creates additional safety concerns.

9.2 Recommendation on Regulatory Action

I do not recommend approval of this application until the following deficiencies are addressed:

1. The sponsor must demonstrate substantial evidence of efficacy of NTG ointment in relieving pain from chronic anal fissure in a new trial of convincing statistical significance ($p < 0.01$) or two trials at the usual level of significance ($p<0.05$).

2. For trials the primary endpoint analysis must be pre-specified operationally such that no variations are determined after any trial data are available. An analysis plan for secondary endpoints should also be pre-specified that preserves an overall alpha of 0.05 for all secondary analyses.

3. Randomization should be done centrally. Dropouts after randomization but prior to initiating treatment should be avoided entirely.

4. Patients should be followed for endpoint evaluation until the time of the primary endpoint evaluation regardless of discontinuing treatment. The handling of missing data must be unambiguously specified in the protocol.

5. A global assessment of pain (all pain, including headache and anal fissure pain) must be included in the evaluation.

6. For patients with tachycardia or bradycardia, dizziness, or lightheadedness, vital signs should be obtained preferably when the patient is symptomatic and, if abnormal, followed until the abnormality resolved. Detailed information must be collected regarding all serious adverse events corresponding to Medwatch reporting requirements.

7. Vital signs should be recorded around the time of estimated peak effect after chronic administration. To estimate intra-individual variability, these measurements should be repeated on a different day in a subset of patients. The administration of the study drug should be performed by the patient without special coaching.

8. Recruitment for any new trials should include reasonable representation of the elderly and patients with chronic diseases such as hypertension and heart failure.

9.3 Recommendation on Postmarketing Actions

Because I do not recommend approval I can not recommend postmarketing actions.

9.4 Labeling Review

Because I do not recommend approval I have not done a labeling review.

9.5 Comments to Applicant

The deficiencies listed in Section 9.2 should be communicated to the sponsor.

Appendices

9.6 Review of Individual Study Reports

9.6.1 Study CP125 03-03-01, A Study to Determine the Effect of CP125 Ointment on the Pain Associated with a Chronic Anal Fissure

9.6.1.1 Protocol, Amendment and Post Hoc Changes

The initial protocol for this study is numbered CP125 03-02-01 and dated April 2, 2003. This study was not amended. The NDA submission does not identify any post hoc changes to the protocol.

COMMENT:

- I note that the protocol states the planned study size as 150 while data from 193 subjects were analyzed. The NDA submission did not comment on this discrepancy. The sponsor explained in a letter than the protocol synopsis indicates that "at least 150 subjects" will be enrolled (I confirmed) and that the trial was proceeding rapidly so that it was difficult to tell investigators not to enroll subjects who had already started screening procedures. Note that randomization was done locally and not through a central randomization center or system.

- I discuss in the Results section the post hoc interpretations of variations in the data analysis that were not completely specified in the protocol.

- The study did not follow exactly the protocol description of study number assignments. I describe the variation in Section 9.6.1.2.8.1 Number of Subjects, Randomization, and Blinding.

9.6.1.2 Study Design

This was an international, multi-site, randomized, double-blind, placebo-controlled parallel group study.

9.6.1.2.1 Objectives

The primary objective was to determine the effect of NTG ointment vs. placebo on pain associated with anal fissure. Another objective was to determine the effect of NTG ointment on healing of anal fissure. The safety and tolerability of NTG ointment was to be elucidated, particularly with regard to headache.

9.6.1.2.2 Inclusion and Exclusion Criteria

The inclusion criteria were the following (note the qualifying entry criteria in 1 and 4 below):

1. single anal fissure
2. informed consent
3. aged 18-75
4. history of anal pain at least three days a week for at least 30 days, confirmed sentinel pile, visual analog score (VAS) =35 mm and historical categorical pain score of moderate or severe for each of 2 days prior to treatment
5. willingness to forego other anal treatment drugs during study
6. willingness to limit sitz baths to one per day
7. practicing birth control if female of child-bearing potential
8. willingness to provide blood and urine samples

The exclusion criteria were the following:

1. more than one anal fissure
2. fistula-in-ano
3. anal surgery within 30 days
4. any other experimental study within 30 days
5. lacking suitability to participate per investigator
6. positive urine screen for illicit drug
7. allergy to NTG or vehicle constituents
8. hypotension, hypovolemia, increased intracranial pressure, aortic or mitral stenosis, hypertrophic obstructive cardiomyopathy, constrictive pericarditis or tamponade, marked anemia, or closed angle glaucoma
9. receiving NTG by any route
10. pregnant or nursing female
11. anal abscess
12. inflammatory bowel disease
13. pelvic radiation
14. fixed anal stenosis
15. immunocompromise
16. unwillingness to discontinue PDE5 inhibitor

9.6.1.2.3 Study Plan

Patients were to be screened for eligibility over five days and then randomized to double-blind active treatment or matching placebo. Study medication was to be applied intra-anally every 12 hours as described in the next section. Patients were to record in a daily diary of the following:

- 24-hour average pain and pain on defecation on a visual analog scale (VAS)
- times when study medication was applied
- number of sitz baths
- headache start time, stop time, and severity
- time and number of acetaminophen tablets consumed
- all concomitant medications including fiber

Patients were to be treated for 56 days with clinic visits at days 7, 21, 35, and 56. Anal fissure healing was to be determined at each study visit by a trained observer blinded to other study aspects. Follow-up was to continue by phone every 3 months for 12 months.

9.6.1.2.4 Dosage, Duration, and Adjustment of Therapy

The ointment was to be was to be applied about very 12 hours for 56 days. Patients were provided with a measuring device. The contents of the measuring device were to be delivered onto the tip of a finger covered with a finger cot. That finger was to be inserted into the anal canal up to the first interphalangeal joint and the ointment applied to the anoderm. No adjustments to therapy were specified.

9.6.1.2.5 Concomitant Therapy

Patients on dietary fiber supplements or stool softeners could continue them at their usual dose but new use was prohibited. Acetaminophen 650 mg PO could be used as rescue medication for a headache occurring within 30 minutes of NTG ointment use but not more than 8 doses during the first 21 days. Sitz baths were limited to one per day. Other NTG, NSAID, and aspirin (except low dose aspirin for cardiovascular prophylaxis) use was prohibited.

9.6.1.2.6 Efficacy Endpoints

9.6.1.2.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the rate of change of the 24-hour average pain intensity over a 21-day treatment period. See the Statistical Considerations section below for more details on the analytic approach and handling of missing data. Patients were asked to record at bedtime their pain symptoms on a visual analog scale (VAS). The VAS was a 100 mm line marked "no pain" at the left end and "worst pain imaginable" at the right end. Patients were to complete two scales each bedtime, one for the average amount of pain experienced during the preceding 24-hour period and another for the amount of pain experienced during the last bowel movement.

9.6.1.2.6.2 Secondary Efficacy Endpoints

The secondary efficacy endpoint was the time to 50% improvement in the three-day average (moving window) of 24-hour average pain intensity measurements. Tertiary endpoints included rate of change of pain intensity over a 56-day treatment period, rate of change of pain intensity during the last bowel movement over the 21-day period, rate of change of pain intensity during the last bowel movement over the 56-day period, and complete healing over the 56-day period.

COMMENT: The need to use a statistical method, such as Holm's stepdown method, to maintain Type I error at 0.05 for the secondary endpoints was communicated to the sponsor in a letter dated May 16, 2003.

9.6.1.2.7 Safety Endpoints

Safety was evaluated through adverse events (AEs), routine safety labs, vital signs, physical examinations, and ECGs. Headache start time, stop time, and severity were to be recorded in the patient's daily diary.

9.6.1.2.8 Statistical Considerations

9.6.1.2.8.1 Number of Subjects, Randomization, and Blinding

The planned study size was 150 (75 per group). The sample size was calculated using a mixed-effects regression model, with type 1 error of 5%, power of 80%, residual variance of 102.53, projected placebo mean at 21 days of 24.95 and SD 18.61, and projected NTG ointment mean of 15.59 and SD 15.79. With these parameters 53 completer participants per group were estimated. A group size of 75 was selected to allow for dropouts.

Patients were randomized based on a computer-generated randomization schedule prepared by FRI Solutions, Inc. Randomization was stratified by center and balanced using permuted blocks of size 4. Blinded labeling of study drug and matching placebo (vehicle ointment without NTG) was prepared by BlisTech Corporation. The label included a tear-off portion having a concealed area containing the drug identity.

Principal investigators were to be assigned a three number identification code. Subject numbers were to be issued sequentially in the order subjects were enrolled starting at 001. The case report forms were to be numbered with the combination of the investigator code and sequential subject number, e.g., 301-001.

To check whether unblinding had occurred patients and investigators were to be asked verbatim the following questions (from page 36 [original numbering] of the protocol) on day 21±2:

- Patient: "During your participation in the study, which treatment do you think you received nitroglycerin ointment or placebo ointment?

- Investigator: "Which treatment do you think the participant received during the study, nitroglycerin ointment or placebo ointment?"

COMMENT: See comments on numbers of patients in Section 9.6.1.1 Protocol, Amendment and Post Hoc Changes and on how patient numbers were really assigned and randomization done in Section 9.6.1.3.1.2 Good Practice, Monitoring, and Protocol Deviations.

9.6.1.2.8.2 Analysis Cohorts and Missing Data

The protocol does not define an analysis cohort. It states that "With respect to missing data, all available data from each placebo participant and each treatment participant who drops out for a reason other than headache will be used in the analysis." It states further that "for participants treated with active CTM who leave the study due to headache, the last available observation (plus a simulated random error component based on the variance components structure from the model) will be carried forward to all subsequent measurement occasions… The random error component will be simulated from a normal distribution with mean zero and variance equal to the residual variance from the model estimated from all available data."

COMMENT: This approach for insuring appropriate variance for last observation carried forward (LOCF) was suggested to the sponsor in a teleconference on March 20, 2003.

9.6.1.2.8.3 Primary Analysis

The primary outcome measure proposed was the rate of change of the 24-hour average pain intensity over a 21-day treatment period. The measure was to be tested as the linear component (slope) of the treatment-by-week interaction in a generalized mixed-effects regression model, with random intercept and linear time-trend, using SAS MIXED.

9.6.1.2.8.4 Secondary Analyses

Secondary analyses of rates of change also were to use the mixed-effects regression model as for the primary analysis. However, for the secondary analyses a quadratic term was to be added. Analysis of the secondary endpoint time to 50% improvement was to be tested using a "Cox log rank test."

COMMENT: The protocol does not specify how the secondary analyses will be adjusted for multiplicity.

9.6.1.3 Results

9.6.1.3.1 Conduct

9.6.1.3.1.1 Sites, Investigators, and Study Dates

Twenty-nine sites in five countries enrolled 193 patients: US (19%), Germany (13%), Israel (0.5%), Russia (41%), and Serbia (26%). The enrollment on the arms was balanced within countries with the exception of the US, in which 21 patients received placebo and 16 received NTG ointment. The first patient was enrolled on June 16, 2003, and the study was completed on December 16, 2003.

COMMENT: Two (024 with 20 patients and 041 with 16 patients) of the three largest sites had better than average results with NTG ointment. Eliminating them from the analyses eliminated the small benefit from NTG ointment found by the sponsor. I recommended to DSI to audit these sites. Both of them were located in Serbia.

9.6.1.3.1.2 Good Practice, Monitoring, and Protocol Deviations

The study was conducted in accordance with Good Clinical Practices. The sponsor audited three sites in Serbia and Montenegro, five sites in Russia, and one site in Germany. The sponsor closed site 043 in Russia after the first monitoring visit revealed a large number of protocol violations. Screening assessments were incomplete and no drug exposure, efficacy, or safety information was collected. The sponsor classified the four subjects (two per arm) at this site as withdrawn for administrative reasons.

Most of the other protocol deviations were minor other than a few documented in the next section regarding Disposition of Subjects. The most frequent deviation (74 placebo and 56 NTG) were study visits outside of the protocol-specified window. Inclusion/exclusion criteria not being met was reported in 17 instances for placebo patients and 20 instances for NTG patients. The most frequent of these deviations was a lab test result outside of the normal range (23 of the 37 instances). Noncompliance (<70% or >130% by weight or missed doses) was reported in 52 instances for placebo patients and 49 instances for NTG patients. Acetaminophen was used for headache by 24 placebo patients and 34 NTG patients.

Randomization was not done centrally but at each individual site. Study drug in blocks of four numbered sequentially was distributed to each site. The sites were to select the next available sequential number for the next patient randomized. One site (033) appears to have used a higher block prior to using a lower block and another site (035) appears to have assigned a block starting with the highest number and working down. For the highest subject number (296) for this block from site 035 the randomization date is reported as August 31 but the date of first treatment is reported as July 31—other dates in the data files are consistent with July 31. Two entries (block 13, subject 49, site 008; and block 82, subject 326, site 26) were assigned to patients but results for these patients are not reported. For the first the sponsor reported that the inclusion criteria were not met and the study drug was retrieved. For the second the sponsor reported that the entry was "reserved" for a patient but the patient was not enrolled because lab tests were incomplete and were not completed prior to enrollment closing. Both of these entries were NTG study drugs.

At about day 21 the patients and investigators were asked questions regarding whether the patient was receiving NTG ointment or placebo. The sponsor's analysis of these questions is shown in Table 19: Sponsor's Analysis of Unblinding Questions.

Table 19: Sponsor's Analysis of Unblinding Questions

			Placebo N=98		Cellegesic NTG Ointment 0.4% N=89	
Assessment			**n**	**(%)**	**n**	**(%)**
Subject:	"During the study did you receive nitroglycerin ointment or placebo?"	Nitroglycerin Ointment	64	(65.3)	64	(71.9)
		Placebo	19	(19.4)	9	(10.1)
		Unable to Decide	12	(12.2)	9	(10.1)
		Missing Assessment	3	(3.1)	7	(7.9)
Investigator:	"During the study do you believe the participant received nitroglycerin ointment or placebo?"	Nitroglycerin Ointment	42	(42.9)	56	(62.9)
		Placebo	34	(34.7)	12	(13.5)
		Unable to Decide	19	(19.4)	14	(15.7)
		Missing Assessment	3	(3.1)	7	(7.9)

DSI audited two sites in Serbia. The DSI inspector judged data from both sites to be acceptable. The inspector noted minor problems at both sites with dosage (dosage exceeded probably because of inadequate instruction) and at one site with recordkeeping accuracy. At one site investigator records for patient dose compliance indicate that doses varied from 375mg by 20% or more at 44 visits of the total of 80 evaluation visits. At the other site the compliance was as high as 252%, 330%, and 397% in three patients.

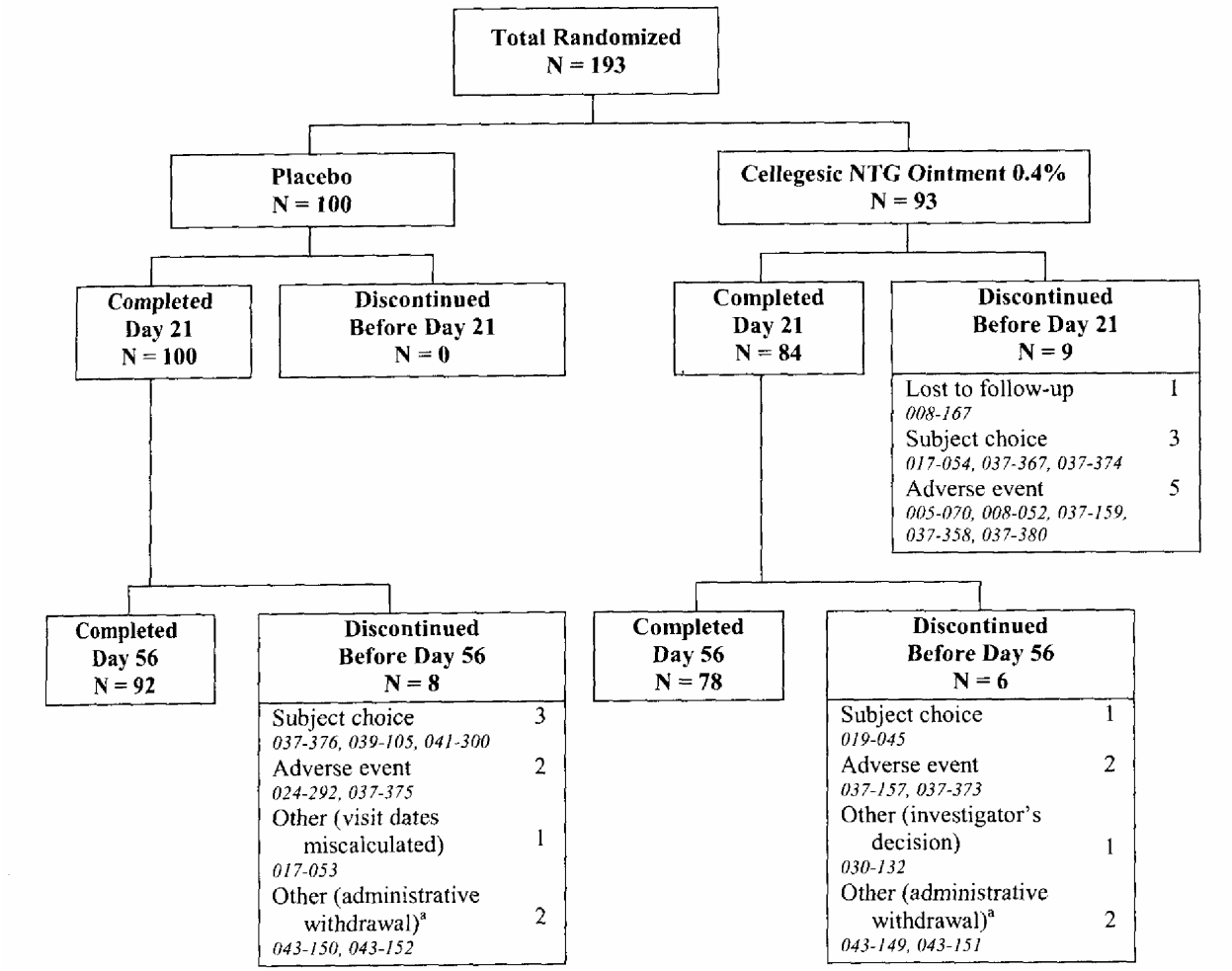
The DSI inspector asked the investigators why there was such a dramatic improvement in some subjects' pain, sometimes within 24 hours of enrollment. The investigators did not have any explanations other than they did see this happen and that it could be a placebo effect. .

COMMENT: The randomization was sloppy. Randomization at the site with a small block size increases susceptibility of breaking of the blinded allocation. There were at least 195 patients randomized rather than 193 as reported by the sponsor.

The analysis of the unblinding questions suggests that there was partial unblinding of the study, particularly from the appraisals by the investigators.

9.6.1.3.2 Disposition of Subjects

The sponsor's figure showing disposition of subjects is given in Figure 2.



[a] Subjects were withdrawn because the site was closed for administrative reasons.

Figure 2: Sponsor's Subject Disposition

My accounting of subject disposition differs from that shown in Figure 2. I count two more patients randomized to NTG as described in the last section and note that one of the patients discontinuing for "patient choice" prior to day 21 did so for increased anal pain. I also believe that it is crucial to show the accounting for the sponsor's primary analysis set of 187 patients and for data completeness. I show my accounting through day 21 in Table 20.

Table 20: Reviewer's Subject Disposition and Data Completeness to Day 21

Category	Placebo		NTG	
	N	Subject IDs	N	Subject IDs
Randomized	100		95	
Ineligible	0		-2	008-049, 026-326
Sponsor's "randomized"	100		93	
Excluded Russian site	-2	043-149, 043-151	-2	043-150, 043-152
Lost to follow-up	0		-1	008-167

Category	Placebo		NTG	
	N	Subject IDs	N	Subject IDs
Subject choice D/C, not dosed	0		-1	017-054
Sponsor's analysis set	98		89	
Subject choice D/C, sponsor censored	0		-1	037-367
Headache D/C, sponsor LOCF	0		-2	008-052, 037-159
Headache D/C, sponsor censored	0		-2	005-070, 037-358
Data complete to day 21	98		84	
*Headache D/C, sponsor LOCF	0		-1	037-380
*More pain D/C, all data used	0		-1	037-374
Sponsor's "completed day 21"	98		82	

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

COMMENT: Note that, in addition to the two patients in each group excluded from the Russian site who failed an audit, 11 patients in the Cellagesic group discontinued before day 21 (the primary endpoint period) but none in the placebo group. (Two of these 11 patients do have diary data complete through day 21.) The Division cautioned the sponsor at a meeting on January 31, 2003, that a large number of dropouts would make interpretation of the study results impossible.

The sponsor's handling of these discontinuations is not entirely consistent with the protocol. The sponsor restricted using LOCF to patients who dropped out for headaches judged to be related to study drug. The protocol states that LOCF will be used for patients discontinuing for headache without qualifying the headache as related to study drug.

I am also concerned that the patient lost to follow-up and the two who discontinued for "subject choice" also had efficacy failure or adverse events. For the primary analysis LOCF must be used for all NTG patients discontinuing for headache as specified in the protocol.

9.6.1.3.3 Demographics and Baseline Characteristics

Demographics and selected baseline characteristics are shown in Table 21. The majority of the patients were white females under the age of 65. The findings on the baseline anal exam are shown in Table 22.

COMMENT: There do no appear to be any substantial demographic or baseline characteristic imbalances.

Table 21: Sponsor's Demographics and Baseline Characteristics

Characteristic	Value	Placebo (N=98)	Cellegesic NTG Ointment 0.4% (N=89)
Sex, n (%)	Male	37 (37.8)	30 (33.7)
	Female	61 (62.2)	59 (66.3)
Race, n (%)	Caucasian	94 (95.9)	84 (94.4)
	Black	1 (1.0)	3 (3.4)
	Asian	0 (0.0)	0 (0.0)
	Hispanic-American or Latino	3 (3.1)	2 (2.2)
	Native American	0 (0.0)	0 (0.0)
	Other	0 (0.0)	0 (0.0)
Age n (%)	≤ 45 years	34 (34.7)	43 (48.3)
	46-64 years	57 (58.2)	38 (42.7)
	≥ 65 years	7 (7.1)	8 (9.0)
(years)	N	98	89
	Mean (SD)	47.7 (10.67)	47.7 (11.48)
	Median	49.0	47.0
	Min – Max	20 – 70	25 – 76
Weight (kg)	N	98	89
	Mean (SD)	78.6 (15.49)	77.5 (16.65)
	Median	76.5	76.0
	Min – Max	50 – 120	44 – 128
	Missing	0	0
Height (cm)	N	98	89
	Mean (SD)	168.3 (9.18)	169.5 (8.96)
	Median	166.5	168.0
	Min – Max	150 – 191	154 – 201
	Missing	0	0
Body Mass Index (kg/m^2)	N	98	89
	Mean (SD)	27.76 (5.084)	26.90 (5.096)
	Median	27.36	25.93
	Min – Max	18.9 – 43.0	16.5 – 41.1
	Missing	0	0
Current Alcohol Use	Yes	25 (25.5)	16 (18.0)
	No	73 (74.5)	73 (82.0)
Current Tobacco Use	Yes	25 (25.5)	16 (18.0)
	No	73 (74.5)	73 (82.0)

Table 22: Sponsor's Baseline Anal Exam Findings

Characteristic	Value	Placebo (N=98)	Cellegesic NTG Ointment 0.4% (N=89)
Anal Fissure,[a] n (%)	Single Anal Fissure	97 (99.0)	89 (100.0)
	More than 1 Anal Fissure	1 (1.0)	0 (0.0)
	Absent	0 (0.0)	0 (0.0)
Fissure Features,[a, b] n (%)	Visible Fibers	47 (48.0)	54 (60.7)
	Indurated Edges	69 (70.4)	68 (76.4)
	Sentinel Pile	97 (99.0)	89 (100.0)
	Hypertrophied Anal Papilla	42 (42.9)	40 (44.9)
Fissure Length (cm)[c]	N	98	88
	Mean (SD)	1.06 (0.774)	1.08 (0.627)
	Median	1.00	1.00
	Min – Max	0.3 – 5.0	0.2 – 4.0

[a] Subjects had to have a single anal fissure and a sentinel pile to be eligible for enrollment.
[b] Subjects are counted in all applicable categories.
[c] Estimated length, not measured length.

9.6.1.3.4 Dosing

Compliance, assessed by weighing the study medication, was slightly higher in the placebo group. The percent of subjects who used from 70 to 130% of the required quantity was 84% in the placebo group and 72% in the NTG group.

9.6.1.3.5 Concomitant Therapy

More patients in the NTG group used acetaminophen (paracetamol) than in the placebo group as shown in Table 23.

Table 23: Sponsor's Concomitant Medications Taken by =5% of Subjects

	Placebo N=98		Cellegesic NTG Ointment 0.4% N=89	
WHO Preferred Term	n	(%)	n	(%)
acetylsalicylic acid	9	(9.2)	6	(6.7)
diazepam	6	(6.1)	6	(6.7)
paracetamol[a]	26	(26.5)	36	(40.4)

[a] United States Pharmacopoeia Dictionary of U.S. Adopted Names and International Drug Names (USAN) name is acetaminophen.

Sitz bath use was similar in the two groups as shown in Table 24. The numbers of patients starting dietary fiber or stool softeners during the study was low, one patient in each group during the first 21 days and one additional patient in the NTG ointment group after day 21.

Table 24: Sponsor's Sitz Bath Use

Time Period[a]	Statistics	Placebo (N=98)	Cellegesic NTG Ointment 0.4% (N=89)	P-value[b]
Days 1 through 21	N	98	89	0.2031
	Mean (SD)	5.2 (7.74)	4.4 (7.37)	
	Median	0.5	0.0	
	Min – Max	0 – 21	0 – 26	
Days 1 through 56	N	98	89	0.4986
	Mean (SD)	12.0 (19.77)	10.3 (17.83)	
	Median	1.0	0.0	
	Min – Max	0 – 56	0 – 64	

[a] Summary statistics were calculated by using the total number of sitz baths recorded for each subject during the indicated time period.
[b] P-values were calculated by using a Wilcoxon rank-sum test.

COMMENT: The greater use of acetaminophen in the NTG ointment group is another confounder of the relationship between NTG ointment use and symptomatic relief.

9.6.1.3.6 Primary Efficacy Endpoint

For the primary efficacy endpoint, rate of change of the 24-hour average pain intensity over a 21-day treatment period evaluated by a generalized mixed-effects regression model, the sponsor reports a P value of <0.0498 (Table 13 of the study report). The mean changes calculated by the sponsor are -24.9 for placebo and -28.1 for NTG, a difference of 3.2 mm favoring NTG on a 100 mm visual analog scale.

However, the sponsor's handling of some patients' data for its primary analysis is not consistent with the protocol specification. The sponsor did not use LOCF for two patients (005-070, 037-358) who discontinued due to headache. For another patient (037-380) the sponsor carried forward the last pain score prior to discontinuing study drug rather than using the pain scores recorded after discontinuing study drug. (See Table 20 for my accounting of subject disposition and data completeness to day 21.) Dr. Hung, the FDA statistical reviewer, performed analyses avoiding these analytic problems. The results of his analyses are shown in Table 25.

Table 25: Statistical Reviewer's Primary Efficacy Analysis – Rate of Change and Mean Change from Baseline in Average VAS Score for Pain Intensity Due to Anal Fissure at Day 21 (the Sponsor's ITT Patient Population)

#	Data Inclusion	Placebo (N=98)	NTG (N=89)	NTG - placebo in slope (± SE)	p-value
1	**Sponsor's primary analysis:** LOCF for discontinuation only due to drug-related headache	-31.0	-34.6	-0.29 ± 0.15	0.0498

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

1 sponsor's primary analysis: impute post discontinuation data only for 008-052, 037-159, 037-380, censor at discontinuation for 005-070, 037-358, 037-367, use all available data for 037-374
2 impute post discontinuation data only for 008-052, 037-159, censor at discontinuation for 005-070, 037-358, 037-367, use all available data for 037-374, 037-380
3 impute post discontinuation data for 008-052, 037-159, 037-380, 005-070, 037-358, 037-367, use all available data for 037-374
4 impute post discontinuation data for 008-052, 037-159, 005-070, 037-358, 037-367, use all available data for 037-374, 037-380
5 impute post discontinuation data for 008-052, 037-159, 005-070, 037-358, censor at discontinuation for 037-367, use all available data for 037-374, 037-380
6 use all available data for 037-380 and 037-374, do not impute missing data for remaining five dropouts
7 delete post discontinuation data, do not impute

COMMENT: The analysis from Table 25 that matches the description of the primary analysis in the protocol and the discussions with the sponsor prior to the NDA submission is #5, with a p value of 0.12. I would argue that the more appropriate analysis is to use all available data, including post-study drug discontinuation data. The analysis corresponding to the latter is #4, with a p value of 0.15. Regardless, by the primary analysis this study fails to show efficacy of Cellegesic NTG ointment for relief of pain with anal fissure.

The evidence for efficacy of NTG ointment from this study is even weaker than the p value of 0.12 implies. This study is plagued by a high dropout rate only in the NTG arm: 11 (12%) randomized patients discontinued before day 21, and 9 (9.5%) have incomplete data through day 21. The Division warned the sponsor that a high dropout rate would make this study uninterpretable. If one does a true ITT analysis, i.e., all randomized patients, and classifies the four patients whom the sponsor excluded from its analysis (excluding the two NTG patients from the Russian site who may be considered legitimate exclusions) as failures (i.e., zero slope pain curves), then the p value would be substantially worse than 0.12. Please see also the FDA statistician's review for a further discussion of the dropouts and their effect upon the interpretation of the study results.

9.6.1.3.7 Secondary Efficacy Endpoints

The one secondary efficacy endpoint was the time to 50% improvement in the three-day average (moving window) of 24-hour average pain intensity measurements. By the sponsor's calculation there was no statistically significant difference between the two groups ($p<0.295$).

The protocol defined four tertiary endpoints (although it did not specify how the analyses of them would be adjusted for multiplicity). Given the statistical insignificance of the primary and secondary endpoints, I did not re-analyze them. I've listed in Table 26 a summary of the sponsor's analyses of the tertiary endpoints.

Table 26: Reviewer's Summary of Sponsor's Tertiary Analyses

Endpoint	Summary	P#
Pain change for 56 days	NTG marginally better by sponsor's analysis	0.0447
Last BM* pain for 21 days	No significant difference	0.0719
Last BM* pain for 56 days	NTG marginally better by sponsor's analysis	0.0306
Healing at 56 days	Placebo 63% vs. NTG 69%†	0.4166

*BM = bowel movement; †Data missing for 1 placebo, 6 NTG patients; # no multiplicity adjustment

COMMENT: The sponsor's secondary analyses are consistent with the primary endpoint results and do not suggest efficacy of NTG ointment. Even the results marginally statistically significant by the sponsor's report would not be with multiplicity adjustment or with including all cases and data rather than the sponsor's selective inclusion as with the primary analysis. Noteworthy is that neither pain nor healing were improved.

9.6.1.3.8 Subgroup Analyses

Because the sponsor's primary endpoint analysis is complex and produces a statistic that is hard to visualize, for subgroup analyses I used a simpler approach of examining the mean change in the pain scores at day 21 with missing data replaced by LOCF or, for patients dropping out for increased pain, an average increase of 25 (the increase for the one patient dropping out for increased pain with a recorded increased score.) For comparison I've listed the overall results for this statistic in Table 27. By the ranksum test the differences in changes in pain scores at day 21 are insignificant ($p = 0.58$).

Table 27: Reviewer's Mean Changes from Baseline to Day 21 in Pain Score

Arm	N	Baseline	Change from Baseline		
			Mean	SD	Median
Placebo	98	54	-31	22	-34
NTG	91	55	-32	25	-35.5

COMMENT: The above analysis shows how little difference in pain scores is evident at day 21.

9.6.1.3.8.1 Region and Country

The mean changes from baseline to day 21 in pain score by country are shown in Table 28.

Table 28: Reviewer's Mean Changes from Baseline to Day 21 in Pain Score by Country

Country	Placebo		NTG	
	N	Change	N	Change
Germany	12	-28	13	-12
Israel	1	6	0	
Russia	40	-38	39	-40
Serbia	26	-25	25	-36
US	21	-29	16	-21

COMMENT: Note that the only country with a substantial improvement in pain scores with NTG is Serbia. US patients fared better with placebo. Serbia had three sites, two of which showed substantial improvement with NTG.

9.6.1.3.8.2 Age and Gender

The mean changes from baseline to day 21 in pain score by age are shown in Table 29 and by gender in Table 30.

Table 29: Reviewer's Mean Changes from Baseline to Day 21 in Pain Score by Age

	Placebo	NTG
=40	-33	-34
41-50	-26	-35
51-60	-36	-30
>60	-25	-25

Table 30: Reviewer's Mean Changes from Baseline to Day 21 in Pain Score by Gender

	Placebo	NTG
Female	-31	-32
Male	-31	-32

COMMENT: There do not appear to be any significant differences in response by age or gender.

9.6.1.3.8.3 Race

The vast majority of patients were white (95%). There are two few patients of other race or ethnic groups to provide meaningful statistics on efficacy by race.

9.6.1.3.8.4 Other Subgroups

There are no other subgroups of particular interest.

9.6.1.3.9 Safety

9.6.1.3.9.1 Exposure

The exposure to NTG in this study was 89 initially, decreasing to 81 at 21 days, and 61 at 56 days. All dosing was the same.

9.6.1.3.9.2 Serious Adverse Events

9.6.1.3.9.2.1 Deaths

There were no deaths during the study.

9.6.1.3.9.2.2 Hospitalizations

One NTG and one placebo patient were hospitalized due to AEs. The NTG patient was a 69-year-old male with a history of T-cell lymphoma treated by surgery and chemotherapy. After treatment with NTG for 23 days he withdrew because of rectal pain. On day 46 he developed abdominal pain, then loose stools and pyrexia. On day 50 he was hospitalized with ascites and partial bowel obstruction due to an abdominal mass. The diagnosis was lymphoma.

9.6.1.3.9.2.3 Other SAEs

The only SAE in the NTG group was the one hospitalization described above.

9.6.1.3.9.3 Withdrawals

Seven NTG and two placebo patients withdrew because of AEs per the sponsor. The reasons for withdrawal of the NTG patients included headache in five (vs. no placebo patients) and burning sensation in two (vs. one placebo patient). One NTG patient (008-052) also had dizziness, bradycardia, and extrasystoles and another (037-380) had tachycardia.

Patient 008-52 who withdrew because of dizziness, bradycardia, and extrasystoles was a 54-year-old Hispanic female with a history of hypertension and dyspepsia taking atenolol/chlorthalidone (?) and Nexium. She developed headache and dizziness starting day 1 and the bradycardia and extrasystoles starting day 8, at which time she withdrew. The bradycardia and extrasystoles are recorded as ended by day 20. There are no other details on these AEs.

Patient 037-380 who withdrew with tachycardia was a 52-year old white female with a history of colon cancer and nephrolithiasis who developed headache and "mild" tachycardia on day 1 and withdrew on day 7. The heart rate and rhythm are not recorded.

COMMENT: The sponsor's analysis for withdrawals does not include patients who withdrew for increased anal pain or those who withdrew for "subject choice".

9.6.1.3.9.4 Other Adverse Events

Overall 81% of the placebo and 90% of NTG patients reported at least one AE. The most common AE was headache, reported by 67% of the placebo patients and 86% of NTG patients. More NTG patients reported severe headaches (34% vs. 3.4%), took medication for it (48% vs. 28%), and had longer symptoms (mean 8 hours vs. 4.3 hours). The second most common AE was upper abdominal pain, reported by 11% of placebo patients and 18% of NTG patients. Cardiac disorders were reported in one placebo and five NTG patients. In addition to the withdrawals for bradycardia and for tachycardia, one other NTG patient experienced bradycardia, one experienced multifocal ventricular extrasystoles, and one experienced "heart pain". There were no reports of hypotension or low blood pressure.

COMMENT: The headache rate was high in the placebo group, although even higher in the NTG group. The higher rate of cardiac symptoms in the NTG group suggests some effect of systemic absorption and bears scrutinizing in the other trials.

9.6.1.3.9.5 Vital Sign Changes

There were no significant changes in SBP or DBP, pulse, or temperature from day 0 to day 21 or day 56.

COMMENT: The protocol does not specify taking vital signs following administration of study drug, so changes at peak drug effect were not captured.

9.6.1.3.9.6 Laboratory Test Value Changes

There were no significant changes or differences between the two groups from screening to last visit for CBC, chemistry panel, and routine urinalysis values.

9.6.1.3.9.7 Electrocardiographic Changes

One NTG patient withdrew because of bradycardia and extrasystoles, the only abnormality considered "clinically significant". Between 72 and 82% of ECGs were considered normal at any time, and the rates of "not clinically significant" abnormalities in both groups decreased slightly from screening to last visit.

COMMENT: ECGs were only evaluated qualitatively and QTc and other interval measurements at peak drug effect were not done. Given the vast experience with oral and topical NTG, a thorough QTc study is not needed.

9.6.1.3.9.8 Events of Special Interest

The one event of special interest that occurred was headache as discussed above. Another event of special interest, hypotension, was not reported.

9.6.1.3.9.9 Safety Subgroup Analyses

The sponsor did not include subgroup analyses of AEs, e.g., by age, gender, race, etc., in the study report. They will be examined in the ISS.

9.6.1.4 Summary

9.6.1.4.1 Efficacy Summary

This study fails to demonstrate efficacy of NTG ointment for reducing anal pain in patients with anal fissure. By the protocol-specified primary analysis the difference in the rate of change in pain through day 21 compared to placebo is statistically insignificant ($p = 0.12$) even for a modified ITT analysis set excluding four randomized NTG patients. The study also failed to show a beneficial effect upon healing of anal fissure.

9.6.1.4.2 Safety Summary

NTG ointment produces headaches, particularly severe headaches, at rates exceeding placebo. NTG ointment also produces more GI symptoms, predominantly upper abdominal pain. There were two withdrawals for cardiac AEs which, while not alarming, have inadequate characterization to be completely reassuring about cardiac safety. The small size of this study precludes a definitive answer regarding cardiac safety.

9.6.1.5 Conclusions

This study does not support approval of NTG ointment for relief of pain of anal fissure.

9.7 Line-by-Line Labeling Review

Because I do not recommend approval of this application, I have not provided a line-by-line labeling review.

REFERENCES

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