

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 21134

ADMINISTRATIVE DOCUMENTS

CSO Approval/Labeling Review

Application: NDA 21-134
Nitrostat (nitroglycerin sublingual) Tablets

Applicant: Parke-Davis Pharmaceutical Research, a division of Warner-Lambert Company

Background: On March 24, 2000, Dr. Lipicky signed an approvable letter for NDA 21-134, requesting final printed labeling identical to the enclosed marked-up draft labeling.

Review: On April 7, 2000, the sponsor submitted final printed labeling identical to the language in the draft labeling with the approvable letter. However, container labels for all three strengths of the tablet (0.3, 0.4, 0.6 mg) were omitted as well as carton labels for the 0.3 and 0.6 mg strengths. I explained the omissions to Ms. Lavonne Lang of Parke-Davis on April 10, 2000 and she agreed to send the missing labeling to the Division.

The final carton and container labels for all three strengths were sent on April 13, 2000. It was noted at that time by Dr. Srinivasachar, that the carton information for the convenience package (4 bottles of 25 tablets each) of the 0.4 mg strength was different in two ways from the carton information for the 100 tablet size of the 0.3, 0.4 and 0.6 mg strength. Specifically, the information "each tablet contains 0.4 mg (1/150 gr) nitroglycerin." is present in the convenience package whereas the other carton labels do not have this information. In addition, the statement "Usual Dosage—See Package Insert for full prescribing information." is different from the statement on the other cartons, which reads "Usual Dosage—0.3 to 0.6 mg sublingually as needed. See package insert for full prescribing information." The sponsor said that the two differences in labeling of the convenience package compared to the 100 tablet size carton labeling of the 0.3, 0.4 and 0.6 mg strengths have been present since 1993, although it was not known why there was a divergence between the convenience package and the 100 tablet carton labeling. I informed Dr. Srinivasachar of the sponsors' comments and he said that the differences were relatively minor and therefore it was not necessary for Parke-Davis to change the carton labeling of the convenience package.

Under the **Pregnancy Category C** section of the labeling, the sentence that begins "No toxic effects on dams..." was missing a period at the end of it. I will convey this omission to the sponsor but will not mention it in the approval letter, as it is a very minor omission.

Comments/Recommendation: There are no other unresolved issues pending for this NDA. An approval letter will be drafted for Dr. Lipicky's signature.


Edward Fromm
Consumer Safety Officer

Ef/4-28-00

cc: NDA 21-134
HF-2 (MedWatch)
HFD-110
HFD-110/EFromm
HFD-110/Blount

CSO NDA Overview
February 8, 2000

NDA 21-134

Sponsor: Parke-Davis Pharmaceuticals Limited

Classification: 3S

Date of Application: June 2, 1999

Date of Receipt: June 3, 1999

User Fee Goal Date: April 3, 2000

Background

Parke-Davis submitted this NDA on June 3, 1999 for nitroglycerin sublingual tablets to be used in the relief of acute attack or prophylaxis of angina pectoris due to coronary artery disease. The related IND []

Sublingual nitroglycerin tablets have been marketed prior to 1938. Parke-Davis has marketed Nitrostat sublingual tablets since the 1970s. They have revised the formulation, however, developing a compressed tablet with improved weight control, content uniformity and physical stability. An approved NDA is required for this change.

Meetings

July 21, 1999: Filing meeting.

October 1, 1998: Pre-NDA meeting (CMC)

August 5, 1993: Guidance on developing an NDA for nitroglycerin sublingual tablets.

Review

Medical Review

Medical Reviewers: Akinwole Williams, M.D. (safety and efficacy)
Shaw Chen, M.D., Ph.D. (secondary review)

Labeling: see Dr. Williams' 2-2-00 review and Dr. Chen's 2-4-00 review for labeling recommendations.

Conclusion: Williams: approvable
Chen: approvable

Biopharmaceutics Review:

Reviewer: Emmanuel Fadiran, Ph.D.

Labeling: None

Conclusion: Dr. Fadiran states in his review that "the Nitrostat tablet formulations are bioequivalent to the reference Nitrostat tablet formulations based on pharmacokinetic data. However, supportive population pharmacokinetic-pharmacodynamic analysis showed that the pharmacodynamic effect for nitroglycerin obtained for the two formulations were similar."

Statistics (clinical)

Reviewer: John Lawrence, Ph.D.

Labeling: none

Conclusion: Dr. Lawrence notes "The new formulation has not been shown to be equivalent to the old formulation. The data suggest that the marketed formulation may, in fact, be superior to the compressed tablet."

Chemistry

Reviewer: Joseph Piechocki, Ph.D.

Labeling: acceptable

cGMP Inspections: Acceptable, September 20, 1999

Methods validation: not needed

Environmental Assessment: exclusion granted

Conclusion: approvable

Pharmacology

Reviewer: Estela Barry, M.S.

Labeling: no changes recommended

Conclusion: approvable

Statistics (preclin): Not needed

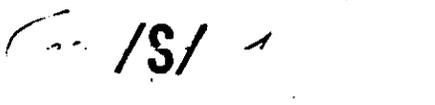
Safety Update: In a September 21, 1999 submission, the firm states that there were no trials ongoing at the time of NDA submission and none have been initiated, so there are no additional data available to comprise a four-month Safety Update to the NDA.

Patent info: included in package

Pediatric info: waiver granted

DSI: Dr. Lipicky said DSI audits were unnecessary.

Debarment Certification: included in package


Edward J. Fromm

cc:

NDA 21-134

HFD-110

HFD-110/E.Fromm/Blount

ef/3/22/00

ITEM 13
PATENT AND MARKET EXCLUSIVITY INFORMATION

13.1. Patent Information

NDA Number: 21-134

Applicant: Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

Active Ingredient: Nitroglycerin

Medical Use: Angina

Strength: 0.3/0.4/0.6 mg

Dosage Form: Sublingual Tablet

Trade Name: NITROSTAT

Generic Name: Nitroglycerin

Patent Statement:

The undersigned declares that to the best of his knowledge, there are no patents that claim the drug, the drug product, or the method of using the drug or the drug product according to the investigations that are relied upon in this application.

Michael J. Atkins
Michael J. Atkins
Counsel Patents 5/19/99

Item 13.2**Request and Justification for 3-Year Marketing Exclusivity**

Warner-Lambert Company requests 3 years of market exclusivity for Nitrostat® (nitroglycerin). Warner-Lambert Company certifies that the active ingredient in Nitrostat, nitroglycerin, meets the criteria for the exclusivity period specified in 21 USC §355(c)(3)(D)(iii), specifically:

1. No drug product containing the same strengths of nitroglycerin has been previously approved for which approval is sought in this application. The active ingredient, nitroglycerin, is contained in other products that have been previously approved.
2.
 - a. Two new clinical investigations, other than bioavailability and bioequivalence studies, were submitted to support this application. Warner-Lambert Company certifies that, to the best of the applicant's knowledge, these clinical studies have not formed part of the basis of a finding of substantial evidence of effectiveness for a previously approved new drug application (NDA).
 - b. The new clinical investigations can be found in Item 8 of the application, NDA No. 21-134, filed concurrently herewith.
3.
 - a. Item 8 of the application, NDA 23-134, filed concurrently herewith, lists all published studies and publicly available reports of clinical investigations known to the applicant that are relevant to support the application.
 - b. Warner-Lambert Company certifies that applicant has thoroughly searched the scientific literature for published studies and publicly available reports on nitroglycerin sublingual tablets.
 - c. Warner-Lambert Company certifies that, in the applicant's opinion, the present application could not have been approved without the new clinical investigations referred to in 2.a. above. The published studies noted in 3.b. above are not sufficient to support the approval of the application.

4. Warner-Lambert Company is the sponsor named in the Form FDA,1571 for IND [] under which the clinical investigations identified in Item 2 above was performed.

**APPEARS THIS WAY
ON ORIGINAL**

EXCLUSIVITY SUMMARY FOR NDA # 21-134

SUPEL # _____

Trade Name Nitrostat Sublingual Tablets

Generic Name Nitroglycerin Sublingual Tablets

Applicant Name PARKE-DAVIS

HFD # 110

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES / NO

b) Is it an effectiveness supplement? YES / NO

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES / NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO /

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO /

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

782-13, 782-16 - Bioequivalence

782-17 - Clinical Efficacy

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
 IND # YES / NO / / Explain: _____

Investigation #2
 IND # _____ YES / / NO / / Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
 YES / / Explain _____ ! NO / / Explain _____

Investigation #2
 YES / / Explain _____ ! NO / / Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / /

NO / /

If yes, explain: _____

 / S /
Signature _____
Title: CSO

 12/29/99
Date

 / S /
Signature of Office _____
Division Director

 2/28/00
Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at time of the last action.

NDA/BLA # 21-134 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-114 Trade and generic names/dosage form: Nitrostat (nitroglycerin sublingual) Tablets Action: AP AE NA

Applicant Parke-Davis Pharmaceutical Research Therapeutic Class 35

Indication(s) previously approved N/A

Pediatric information in labeling of approved indication(s) is adequate inadequate
Indication proposed in this application Acute relief of an attack or acute prophylaxis of angina pectoris due to coronary artery disease.

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? Yes (Continue with questions) No (Sign and return the form)

IN WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

Neonates (Birth-1month) Infants (1month-2yrs) Children (2-12yrs) Adolescents(12-16yrs)

- 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
- 2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
- 3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
 - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
 - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
 - c. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing,
 - (2) Protocols were submitted and approved.
 - (3) Protocols were submitted and are under review.
 - (4) If no protocol has been submitted, attach memo describing status of discussions.
 - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE 4 COMMITMENTS IN THE ACTION LETTER? Yes No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Med. Review - DR. A. Williams (e.g., medical review, medical officer, team leader)

Signature of Preparer and Title ISI CSC Date 4/28/00

Orig NDA/BLA # 21-134
HFD-110/Div File
NDA/BLA Action Package
HFD-006/KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM, CONTACT KHYATI ROBERTS, HFD-6 (ROBERTSK)

HFD-104/TCROSCENZI

ITEM 16.
DEBARMENT CERTIFICATION

Warner-Lambert company hereby certifies that it is not debarred, and did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CDER/ODE-1/DIV CARDIO-RENAL DRUGS

Date: 02/04/2000
From: Shaw T. Chen, M.D., Medical Team Leader, HFD-110
To: Director, Division of Cardioresenal Drug Products, HFD-110
Subject: NDA 21-134, Nitrostat for Angina, Approvability

OVERVIEW

This memorandum and the attached material constitute the Division's recommendation that NDA 21-134, (new) Nitrostat for angina, be approved.

This is an application for a re-formulated tablet of a long-marketed sublingual nitroglycerin, Nitrostat, to be used in the same indications as that approved previously for the other formulations. Compared with the old molded tablets, the new compressed SL-GTN tablets (referred to as "new Nitrostat" in the reviews) claim to have improved weight control, content uniformity and physical/potency stability. As concluded in the relevant reviews, critical biopharmaceutical issues with the new dosage forms have been adequately addressed and the clinical studies were all of proper design and execution. All regulatory reviews have been completed as the date of this memo and there are no unresolved problems that may affect the recommended action. The draft labeling has been edited; no further changes were recommended by either pharmacology or biopharmaceutical reviewers.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS

As described in the reviews by Drs Williams and Dr. Fadiran, the new Nitrostat formulation has been adequately tested in 2 pharmacokinetic/dynamic studies (782-13 and 782-16). The findings are summarized as follows:

- i) The new Nitrostat tablets (0.3mg x2, 0.6 mg x1) were found to be bioequivalent to the approved old Nitrostat product (0.6mg x1) with respect to the metabolites, 1,2-GDN and 1,3-GDN.
- ii) Although the new Nitrostat are *not* bioequivalent with the old tablets with respect to nitroglycerin, this is a well-known phenomenon with other nitroglycerin formulations and has little pharmacodynamic or clinical consequences.
- iii) The pharmacokinetic-pharmacodynamic analyses showed that the two (old and new) Nitrostat formulations produced equivalent dynamic effects on peripheral vasodilation.
- iv) Results of the dissolution and disintegration tests on the new Nitrostat were acceptable.
- v) Since *in vitro* profile of the new Nitrostat 0.4 mg was similar to that of other dose strengths tested, waiver for additional *in vivo* bioequivalence studies on this tablet size can be granted.

There are no specific comments on the relevant sections of draft labeling.

EFFICACY FOR ANGINA

Nitrostat was evaluated for its clinical effects in two double blind, randomized, placebo-controlled, 3-way cross over studies of nearly identical designs.

In the single-center Study 782-15, 35 patients were randomized and completed the study, the results were analyzed for tolerability but not for efficacy. The sponsor claimed that the study was terminated early and the data were neither complete nor verifiable. Thus no efficacy results were presented.

Instead, efficacy data were analyzed only in the second study (782-17), which was a multicenter trial with 55 screened and 40 randomized. In this study, there were 5-8 patients in each one of the 6 treatment sequences (variations of new Nitrostat-old Nitrostat-placebo) in 3 cross over periods. After a screening and a qualifying phase, patients received one single dose (0.6 mg) of study drug (with matching placebo of the other formulation), followed by a treadmill exercise test 5 minutes later. There was a 2-hrs rest for washout between the three treatment periods. For detailed description of the studies, see Dr. William's medical review.

The primary efficacy endpoint in the study was time to moderate angina on the exercise test. Time to onset of myocardial ischemia as measured by changes in ST-segment was the secondary efficacy endpoint. The stated objectives were to show that both Nitrostat formulations are superior to placebo and the two Nitrostat tablets are therapeutically equivalent. However, no explicit criteria for the latter equivalence were specified.

For this short-term study, there was no dropout and all randomized subjects completed the three treatment periods. The data in the following table demonstrate that the new Nitrostat, at 0.6 mg, was significantly more effective than placebo in delaying onset of moderate angina in exercise tests. The time to angina was increased by nearly 0.9 minute over placebo with a p value of 0.0001 (all data of Study 782-17 shown below are from Dr. Lawrence's statistical review):

| New Nitrostat vs Placebo | Estimate | Std error | p-value |
|-------------------------------------|----------|-----------|---------|
| <i>Time to angina (primary)</i> | 0.858 | 0.170 | 0.0001 |
| <i>Time to ischemia (secondary)</i> | 0.917 | 0.269 | 0.001 |

For the secondary endpoint of time to ischemia (1-mm ST changes), the new Nitrostat had similar treatment effect over placebo, as shown in the above table.

The study also showed that the old molded Nitrostat tablet was superior to placebo:

| Old Nitrostat vs Placebo | Estimate | Std error | p-value |
|--------------------------|----------|-----------|---------|
| <i>Time to angina</i> | 0.897 | 0.170 | 0.0001 |
| <i>Time to ischemia</i> | 0.833 | 0.283 | 0.005 |

and there were no significant differences between the two Nitrostat:

| Old vs New Nitrostat | Estimate | Std error | p-value |
|-------------------------|----------|-----------|---------|
| <i>Time to angina</i> | 0.039 | 0.171 | 0.820 |
| <i>Time to ischemia</i> | -0.083 | 0.290 | 0.775 |

Because the differences between the old and the new Nitrostat were in opposite directions for the two endpoints, any speculation on the potential therapeutic difference between the two formulations would be risky.

SAFETY IN ANGINA

There were no qualitative or quantitative surprises in safety experiences of this new formulation, as compared with known effects of previously approved dosage forms. Since this is a new formulation and did not require evaluation as extensive as new molecular entity, rare but more serious events would not be detectable in the relatively limited safety database of this application. The safety sections of the labeling for the new Nitrostat should therefore rely on the previous experience with other dosage forms.

In the two clinical trials, headache, dizziness, and hypotension appeared to be the most common complaints, but not more frequent than the old Nitrostat tablets. Experiences from the non-controlled clinical pharmacology studies in younger subjects were not remarkable (Table 8, Dr. Williams' review). Again, the database is too small to allow any meaningful discussion on the incidence of various adverse events.

There were no serious events, withdrawals due to adverse reactions or deaths reported in the studies submitted.

OVERALL ASSESSMENT

The clinical study (782-17) of the new Nitrostat for angina was well designed and the reviewers did not find any serious deficiency in study execution. The results were interpretable and the conclusions do support the efficacy claims for the new formulation. While it is somewhat disappointing that the efficacy data from the second trial (Study 782-15) were not analyzed, their absence is not critical since:

- i) the new Nitrostat is only a reformulated product of an approved drug with well known pharmacological activities and extensive clinical use, and
- ii) the results of the Study 782-17 were quite convincing ($p \sim 0.0001$).

There were no surprises in safety experiences in the use of the new Nitrostat and the biopharmaceutics of the new formulation has been adequately characterized. Although only one dose (0.6 mg) was studied in the efficacy trial of this application, there is sufficient pharmacokinetic/dynamic correlation with the old formulation (which was approved for 0.3-0.6 mg) that the confidence in efficacy can be extended to other dosages of the new Nitrostat.

While detailed labeling may have to rely on previous experiences with other dosage forms of this well-known nitroglycerin, there is sufficient information to serve as the basis for approval for Nitrostat.

PEDIATRIC/GERIATRIC/FEMALE USE

There are no clinical trials assessing the efficacy or safety of the new Nitrostat in pediatric patients, either completed or in progress. The sponsor claimed that the drug has little potential for use in children and thus did not commit to any study in children with angina.

Efficacy and safety of the new Nitrostat as treatment for angina in the elderly (65 year and older), female and non-Caucasian patients cannot be assessed from the small clinical database. For this well-studied drug, there is no reason not to borrow the subgroup experiences from other similar and different formulations for labeling.

DRAFT LABELING

The draft labeling submitted by the sponsor is consistent with the most recently approved version for the older formulation. Only minor changes were necessary.

CONCLUSIONS

The new Nitrostat appears to be an effective and safe treatment for angina. It is recommended that the new Nitrostat be approved with the edited draft labeling.

TT TST TT

Shaw T. Chen, M.D., Ph.D.

cc:

ORIG: NDA- 21-134

HFD-110

HFD-110/Fromm/Williams

HFD-710/Lawrence

HFD-860/Fadiran/Marroum

HFD-110/SChen/02/04/2000

RHPM Filing Overview

Application: NDA 21-134
Nitrostat (nitroglycerin) Sublingual Tablets

Applicant: Parke-Davis Pharmaceuticals Limited

Application Date: June 2, 1999

Receipt Date: June 3, 1999

Primary Goal Date: April 3, 2000

Secondary Goal Date: June 3, 2000

Background

Sublingual nitroglycerin tablets have been marketed since prior to 1938 and have thus been marketed under grandfather status. Until now, there has been no requirement for an NDA for this drug product. Parke-Davis has marketed Nitrostat sublingual tablets since the 1970s. They have revised the formulation, however, developing a compressed tablet with improved weight control, content uniformity and physical stability. An approved NDA is required for this change. Parke-Davis submitted this application as a 505(b)(1) NDA.

The following meetings were held prior to NDA submission:

Pre-IND: August 5, 1997
Pre-NDA October 1, 1998

Reviewers:

| | |
|----------------------|-----------------------------|
| Chemistry: | Joe Piechocki, Ph.D. |
| Clin Pharm/Biopharm: | Emmanuel Fadiran, Ph.D. |
| Pharmacology: | Estela Gonzelez Barry, M.S. |
| Statistics: | John Lawrence, Ph.D. |
| Clinical: | Akinwale Williams, M.D. |
| Secondary Medical: | Shaw Chen, M.D., Ph.D. |

Review

The applicant conducted one clinical efficacy study to support approval. This appears to be a standard NDA submission with the exception of the Nonclinical Pharmacology and Toxicology section. This section consists of only a summary of literature references describing previous human experience and a summary of subacute and chronic toxicity studies in dogs, rats and mice that was conducted by the U.S. Army.

Since the applicant does not own the data in the preclinical package, it appears that this is a 505(b)(2) application. In discussions with the applicant, however, they have taken exception to this assessment, and a telephone conference call to discuss the issue is being scheduled.

The sponsor has submitted a Debarment Certification and Financial Interests and Arrangements of Clinical Investigators Certification.

The index to the NDA is inadequate. The volume numbering system starts with volume 1 at the beginning of each section, making it incompatible with the FDA Document Room numbering system. I have spoken with the applicant, and they have agreed to submit a revised index.

Summary of Deficiencies

- 1) The issue of whether this application is a 505(b)(2) NDA must be resolved. If it is determined that it is a 505(b)(2) NDA, the applicant is required to submit the appropriate patent certification.
- 2) The index is inadequate. The applicant should submit a revised index that is compatible with the FDA's numbering system.

Recommendation

Both of the above deficiencies can be resolved quickly, and neither constitutes grounds for refusing to file the application. Provided that the reviewers have not identified reasons for refusing to file, I recommend that the application be filed.

David Roeder
Regulatory Health Project Manager

cc: NDA 21-134
HFD-110
HFD-110/PM

Minutes of an NDA Filing Meeting

Date of Meeting: July 21, 1999

Application: NDA 21-134
Nitrostat (nitroglycerin) Sublingual Tablets

Applicant: Parke-Davis Pharmaceuticals Limited

Participants:

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Robert R. Fenichel, M.D., Ph.D., HFD-110, Deputy Division Director
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Shaw Chen, M.D., Ph.D., HFD-110, Medical Group Leader
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Akinwole Williams, M.D., HFD-110, Medical Officer
Estela Gonzalez Barry, M.S., HFD-110, Pharmacologist
Joe Piechocki, Ph.D., HFD-810, Chemist
John Lawrence, Ph.D., HFD-710, Statistician
Emmanuel Fadiran, Ph.D., HFD-860, Clinical Pharmacologist
Michael Skelly, Ph.D., HFD-45, Pharmacologist
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
Edward Fromm, HFD-110, Consumer Safety Officer
David Roeder, HFD-110, Regulatory Health Project Manager

Background

Sublingual nitroglycerin tablets have been marketed since prior to 1938 and have thus been marketed under grandfather status. Until now, there has been no requirement for an NDA for this drug product. Parke-Davis has marketed Nitrostat sublingual tablets since the 1970s. They have revised the formulation, however, developing a compressed tablet with improved weight control, content uniformity and physical stability. An approved NDA is required for this change. Parke-Davis submitted this application as a 505(b)(1) NDA.

Meeting**Regulatory Issues**

Mr. Roeder raised the question of whether this application should have been submitted as a 505(b)(2) NDA. He will follow up on the question with the appropriate FDA authorities. If the status of the application does have to be changed, it could be done quickly and would not constitute a reason for refusing to file the NDA.

Pharmacology

Reviewer: Estela Gonzalez Barry, M.S.

Ms. Barry had no objections to filing the NDA. The applicant submitted literature reports of previous human experience as well as a summary report of U.S. Army toxicology studies. Ms. Barry had completed her review, and it was with her supervisor. She expected it to be in final by August 1, 1999.

Chemistry

Reviewer: Joe Piechocki, Ph.D.

Dr. Piechocki had no objections to filing the NDA. He expects to finish by January 1, 1999. He will request a facility inspection shortly.

Biopharmaceutics

Reviewer: Emmanuel Fadiran, Ph.D.

Dr. Fadiran had no objections to filing the NDA. The applicant had conducted two bioequivalence studies that are summarized in the attachment. The review is expected to be completed by January 1, 2000.

Clinical/Statistical

Medical Officer: Akinwole Williams, M.D.

Statistician: John Lawrence, Ph.D.

The medical officer and statistician did not object to the filing of the NDA. The NDA contains one clinical study report of 55 patients. Since they only studied one dose, the bioequivalence data will be important in evaluating the efficacy.

Dr. Lipicky asked that a joint clinical/statistical review be done. This review is expected to be completed by January 1, 2000.

DSI

DSI audits are not necessary.

Secondary Medical Review

Reviewer: snaw Chen, M.D., Ph.D.

Dr. Chen expects to complete his review by January 15, 2000.

Conclusion

The application will be filed.

Minutes Preparation: /S/
David Roeder

Concurrence Chair: /S/
Raymond Lipicky, M.D. ✓

dr/8-18-99

cc: NDA 21-134
HFD-110
HFD-110/DRoeder/EFromm/SMatthews

MEETING MINUTES

OCT 8 1998

Date: October 1, 1998

Subj: IND [] Nitroglycerin Sublingual Tablets (new formulation)
Pre-NDA Meeting (CMC)

Sponsor: Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company

Meeting Chair: Charles Hoiberg, Ph.D.
Sponsor Lead: Philip Simonson, Ph.D.
Recorder: Gary Buchler

Attending:

Parke-Davis/Warner-Lambert

| | |
|------------------------|---|
| Sean Brennan, Ph.D. | VP, Worldwide Regulatory Affairs, CMC (PD) |
| Jane Daniel | Pharmaceutical Technology (WL) |
| Mary Oates, Ph.D. | Section Director, Analytical Tech Laboratories (WL) |
| Philip Simonson, Ph.D. | Senior Manager, Worldwide Regulatory Affairs (PD) |
| James Strand, Ph.D. | Senior Clinical Scientist, Clinical Pharmacology (PD) |

FDA

| | |
|------------------------------|--|
| Charles Hoiberg, Ph.D. | Director, Division of New Drug Chemistry I, HFD-810 |
| Kasturi Srinivasachar, Ph.D. | Team Leader, Cardio-Renal Division, HFD-110 |
| Joseph Piechocki, Ph.D. | Chemistry Reviewer, HFD-110 |
| Emmanuel Fadiran, Ph.D. | Biopharm. Reviewer, Division of Pharmaceutical Eval. I |
| Gary Buchler | Project Manager, HFD-110 |

BACKGROUND

Parke-Davis has been experiencing problems with content uniformity and assay of the current formulation of nitroglycerin sublingual tablets (Nitrostat) for some time. The marketed formulation is a molded tablet (alcohol granulation). Since this product is marketed under a grandfathered status, it has no approved application. This product was also the subject of Remedial Action Plan (RAP) under the Consent Decree of August 1993. For these reasons, the firm decided to reformulate the product using direct compression and make it the subject of a New Drug Application (NDA). They plan to submit their NDA in the first quarter 1999.

An internal pre-meeting was held on Monday, September 21, 1998 to discuss the firm's proposed issues. In addition to the issues identified by the firm for discussion, other issues were identified and these were discussed with Parke-Davis representatives by Dr. Piechocki prior to the meeting.

DISCUSSION ISSUES

- Use of a disintegration test for product release

The firm proposed to use a disintegration test for product release. Dr. Fadiran discussed this proposal with his supervisors and they decided that, absent correlation between the disintegration testing and the dissolution testing, the firm should use dissolution testing for product release. The firm contended that disintegration testing was more representative of how the product is used. They presented some preliminary dissolution data comparing the two formulations (old molded and proposed compressed). Dr. Fadiran said that, from the data presented, it seemed that a dissolution specification in the minute range could be developed.

ACTION: The firm will develop a validated dissolution method, specification and media for the new formulation of nitroglycerin sublingual tablets. This dissolution test should be incorporated into the stability protocol.

- Clonitrate Compound

Dr. Piechocki inquired about the source of chlorine in the clonitrate degradant. The firm said they have not done enough work to identify the source of chlorine. The firm was informed that the Agency would like to know if the chlorine appears in the nitroglycerin raw material purchased for the manufacture of the tablets. It was suggested that the firm could compare the nitroglycerin procured from the new source with that purchased from their former supplier for impurities.

ACTION: The firm will address the source of chlorine in the NDA.

- Waiver for imprinting tablets

The firm cited the following regulation relating to request for an exemption from imprinting regulations according to 21 CFR 206.7(b)(1) which states:

For a drug subject to premarket approval, FDA may provide an exemption from the requirements of 206.10 upon a showing that the product's size, shape, texture, or other physical characteristics make imprinting technologically infeasible or impossible.

The firm stated that their proposed tablet would weigh 36 mg, the same weight as their presently marketed tablet. The marketed tablet is not imprinted. They do not see how they could imprint the proposed tablet because of its size.

ACTION: The firm will provide samples of the currently marketed tablet and the proposed tablet and a rationale for not being able to imprint as per 206.7(b)(1). A decision will be made as soon as possible as to whether the tablets have to be imprinted.

- Proposed post-approval stability protocol

For post-approval stability testing, the firm proposed testing the first three commercial lots of each strength and package size and then one additional lot for each strength and package size per year.

At the time of NDA submission, they will have 18 months of real time stability on 2 scale-up batches and 12 months real time stability on 9 batches.

ACTION: The proposed stability protocol was acceptable.

- Impurity and degradation product methods and specifications

The firm stated that they will continue to test the product according to USP specifications. They have applied tighter limits for content uniformity, and they will petition the USP to accept their tighter limits.

ACTION: The firm was told that we must know how the specifications were derived. They were told to define the dinitro degradants/impurities and to specify what lactose is used when they set the specifications.

- Proposed 24 month expiration dating period

ACTION: The expiration dating period will be based on the NDA review of the submitted data (see above).

- Acceptance criteria for standards

ACTION: The firm was asked to provide a justification to support the 3% acceptance criteria for the standards. The use of standard solutions that are not accurate is unacceptable for the generation of release or stability data.

Minutes taken by / S / 10/8/98

Gary Buehler

Concurrence, Chair / S / 10/19/98

Charles Hoiberg, Ph.D.

Orig IND
HFD-110GBuehler
HFD-110 SBenton
HFD-150 CHoiberg

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|-----|----------------|---------|
| RD: | EFadiran | 10/5/98 |
| | JPiechocki | 10/7/98 |
| | KSrinivasachar | 10/5/98 |
| | CHoiberg | 10/8/98 |