CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89884

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING

Original Amendment (Major)

DRAFT

DATE OF REVIEW: March 10, 1995

ANDA #: 89-884 (0.2 mg/hr)
89-885 (0.4 mg/hr)
89-886 (0.6 mg/hr)

NAME OF FIRM: Hercon Laboratories

NAME OF DRUG: Generic - Nitroglycerin Transdermal System, 0.2 mg/hr, 0.4 mg/hr and 0.6 mg/hr

DATE OF SUBMISSION: December 8, 1994 [Container labels & package insert labeling] and April 29, 1994 [Patient package insert]

COMMENTS:

General Comment:

a. Delete the terminal zero following a decimal point when expressing the size of the size.

b. We have concerns about the extremely similar labeling between these unapproved applications and your pending supplemental applications for(We believe that such similarity in the labeling for these two inequivalent products will pose a selection problem for substitution by the pharmacist. Please comment and/or revise accordingly.

c. In accord with 21 CFR 201.57(f)(2), make the following revision to your professional package insert:

Reprint the patient information brochure at the end of the professional package insert (i.e., after the HOW SUPPLIED section).

Containers: 0.2 mg/hr, 0.4 mg/hr and 0.6 mg/hr

A. Pouch

1. We encourage you to differentiate between your different product strengths by using boxing and/or contrasting colors.

2. Front panel

Revise as follows:

a. Prominently display the size of the system in parenthesis. For example:

0.4 mg/hr
(___ cm^2)

b. Each ___ cm^2 contains ___ mg of nitroglycerin ...

c. APPROXIMATE RATED RELEASE *IN VIVO* ___ mg/hr

B. Immediate patch - Satisfactory

Carton: 30's

1. Front Panel

See comments under Container (Pouch).

2. Left Side Panel

Usual Dosage -

... of 10 to 12 hours; unless otherwise directed by your physician.

3. Right Side Panel

a. Add the following to the storage instructions; as seen in your insert labeling and by the innovator:

Do not refrigerate

b. We note that you have not included any pictorials, as does the innovator, which would aid in the safe use of this product. Please include.

Patient Package Insert:

1. We note you have not included a copy of the diagrams which are to appear in the Patient Package Insert, please comment.

2. Patient Instructions #1 -

Add the following as the first sentence.

Each Nitroglycerin Transdermal System is individually sealed in a protective package. Open the ...

3. Patient Instructions # 4 -

Revise as follows:

... the backing (which is still in place) to avoid touching the sticky side of the patch.

4. Add the following to the storage recommendations:

Do not store the patch outside the individual package. Apply patch immediately upon removal from the protective package.

Insert:

1. Delete "Prescribing Information" found above the "DESCRIPTION" section heading.

2. DESCRIPTION

a. Paragraph 3 -

... has delivered approximately ...

b. We note, you have indicated that your nitroglycerin transdermal system contains the nitroglycerin in a laminated polymer matrix. This is not consistent with the statement on your carton labeling, which indicates that the nitroglycerin is contained in a polymer adhesive. Please revise the physical description and the inactive ingredients accordingly.

3. WARNINGS

Paragraph 2 -

... harmless in itself, but ...

4. PRECAUTIONS

a. General

Paragraph 5 -

... patients had decreased exercise tolerance ...

b. Information for Patients

Add the following sentence to the end of this subsection:

See Patient Information at the end of insert.

c. Carcinogenesis, Mutagenesis, and Impairment of Fertility

Combine the second and third paragraphs into one paragraph.

d. Pediatric Use

... in pediatric patients have not ...

5. ADVERSE REACTIONS

a. Relocate the third paragraph "Allergic reactions... ", to be the second paragraph of this section.

b. Revise the paragraph referring to "methemoglobinemia" to read as follows:

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred (see OVERDOSAGE).

[NOTE: This is the third paragraph in this section].

c. Relocate the last paragraph, "Application-site irritation ...", to be fourth paragraph of this section.

6. Item Applied (see K-Line) 6/14/95 Please add a description of the transdermal patches, including any device on patch printing.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise container labels, carton and insert labeling and then prepare and submit in final print.

NOTE TO THE CHEMIST:

1. The firm has made revisions to the DESCRIPTION section. Do you concur? [i.e. nitroglycerin delivery rate] yes.

2. In the third paragraph of the DESCRIPTION section, the firm indicates that "After 12 hours, for example, each system has delivered 7% of its original content of nitroglycerin". The manufacturer of NITRO-DUR and TRANSDERM-NITRO patches release "approximately 6% . "Do the Hercon's patches release "7%" or "approximately 7%"? Please see my review delivered 6.66 %.

3. We are requesting the firm to revise the physical description and the inactive ingredients of their product. See comment #2b under Insert. Do you concur? yes.

FOR THE RECORD: 6/14/95

1. Nitro-Dur® manufactured by Schering-Plough (Key Pharmaceuticals, Inc.), revised 10/93 and permitted 12/30/93, used for package insert labeling model.

Comments for the container labels, carton and patient

information insert/leaflet labeling may reflect either Nitro-Dur and/or Transderm-Nitro labels and labeling.

2. This drug product is not listed in the USP.

3. No patents or exclusivity are pending.

Jacqueline White, Pharm.D.

cc: ANDA 89-884
89-885
89-886 [illegible]
HFD-613/JWhite/JGrace/JPhillips (no cc)
mpd/5/8/95; 89884DEC.94
Review
final

JPhillips 6/[illegible]

Telephone Conversation Memorandum

ANDA: 89-884
89-885
89-886

DRUG: Nitroglycerin Transdermal Systems 0.2 mg/hr, 0.4 mg/hr and 0.6 mg/hr

FIRM: Hercon Laboratories Corporation

PERSONS INVOLVED: Tom Atkins, Hercon
Tim Ames, FDA

PHONE NUMBER: 717-764-1191

DATE: July 31, 1998

Firm called and following deficiencies related:

1. Please submit executed batch records and batch sizes for lot# L0557NG/614 (0.2 mg/hr) and lot#L0557NG/612 (0.4 mg/hr) products (total coating mixture as kg, laminate size cm^2 and finished product units).

2. Please refer to the letter dated June 24, 1998 from the Division of Bioequivalence and revise and resubmit your finished product release specifications and stability testing protocol to incorporate these dissolution testing specifications:

Sampling schedule	limits
0.25 hr	%
0.5 hr	%
1.0 hr	%
4.0 hr	%

Mr. Atkins indicated he would submit the requested information to the respective ANDAs as soon as possible.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Branch 6, OGD

/S/

cc: ANDA 89-884, 89-885, 89-886
Division file (3)
HFD-617/TAmes/PHONE.182
File: X:\new\firmsam\hercon\telecons\phone.182

TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **89-884 (0.2 mg/hr)** Dates of Submission: **June 26 and**
89-885 (0.4 mg/hr) **July 9, 1998**
89-886 (0.6 mg/hr)

Applicant's Name: **Hercon Laboratories Inc.**

Established Name: **Nitroglycerin Transdermal System**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? YES

Container Labels:

Pouch - *Satisfactory as of June 26, 1998 submission.*

Immediate Patch - *Satisfactory as of July 9, 1998 submission.*

Carton Labeling: (30s)
Satisfactory as of June 26, 1998 submission.

Professional Package Insert Labeling:
Satisfactory as of June 26 and July 9, 1998 submission.

Patient Package Insert Labeling:
Satisfactory as of June 26 and July 9, 1998 submission.

Revisions needed post-approval: Encourage better differentiation of the strengths.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Transderm-Nitro

NDA Number: 20-144

NDA Drug Name: Nitroglycerin Transdermal System 0.2 mg/hr.

NDA Firm: Summit Pharmaceuticals (Novartis)

Nitro-Dur® (Schering Corporation) was used as the model to review this application. NDA 20-145/S-009 was approved 2-7-96. The professional insert revision date is 7/95.:

Has this been verified by the MIS system for the NDA? YES

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the container label, carton and patient information insert labeling: Nitro-Dur and/or Trans-Derm Nitro labels and labeling.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.		x	
Is this name different than that used in the Orange Book?	x		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
PROPRIETARY NAME - NONE			
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	

Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	x		
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths? - The firm has committed to color coding in FPL		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?			
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?			
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) - *BUT SEE NOTES TO THE CHEMIST	x*		
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			x
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?			
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			x

Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			x
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES TO THE CHEMIST

1. Do you concur with comments 3(b)(i, ii and iii) under DESCRIPTION? (These are from a previous review.)

   b. DESCRIPTION:

      i. Add the statement, "The inactive ingredients are: polyester film, silicone and acrylic adhesive with a cross linking agent".

      ii. Revise the last paragraph to read as follows:

      Each system contains nitroglycerin in acrylic based polymer adhesive with a cross-linking agent to provide a continuous source of active ingredient. The nitroglycerin transdermal system comprises three layers; 1) the outer backing which is composed of a polyester film and is printed with the name of the drug and strength; 2) nitroglycerin in acrylic-based polymer adhesive; 3) a protective peel strip which covers the second layer and must be removed prior to use. Each system is sealed in a paper polyethylene-foil pouch.

      iii. Diagram

      We encourage you to revise the description of your layers to read as follows:

      OUTER BACKING
      (impermeable)
      SECOND LAYER
      (nitroglycerin in adhesive)
      PROTECTIVE PEEL STRIP
      (release liner)

Chemist/Sema response: Yes

The firm did not make the revision under (i.) above. I asked Sema about it and she said they need to do it so I repeated the comment from the previous review to the firm.

As far as (ii.) goes above the firm has revised as shown below:

The Nitroglycerin Transdermal System comprises 3 layers: 1) a transparent outer backing layer composed of a composite plastic film and is printed with the name of the drug and strength; 2) nitroglycerin in acrylic-based polymer adhesive with a cross-linking agent; 3) a protective white, translucent peelable liner which covers the second layer and must be removed prior to use. Each system is sealed in a foil-lined pouch.

I spoke to Sema about this and she said that what the firm has is okay.

2. We requested the firm to list the imprinting ink used on their patch 2 reviews ago. The firm indicated in their response that the imprinting ink contains printing, and that the dried printed ink contains only . Is this acceptable?

Chemist/Sema response: Yes, if it is not it is not necessary to include inactives, but they still have to provide components of the ink.

I discussed this issue with J. White. She did not ask the firm for this information in the last review (but had in the previous review). Her discussion with UV revealed that UV would not make an issue of this (from a chemistry standpoint) if the firm does not do this and if labeling feels that it is not needed then the firm does not need to do it. Previous discussions between J. White and C. Hoppes were concluded with the decision that since the drug product was not to be taken orally and since the firm has stated that the backing is impermeable, we would not ask the firm for this.

FOR THE RECORD: (portions taken from previous review)

1. Label and labeling models:

-Insert labeling - Nitro-Dur® manufactured by Schering-Plough (Key Pharmaceuticals, Inc.), revised 7/95 and approved 2/7/96.
NOTE: Nitro-Dur insert labeling is the most current approved

insert labeling for nitroglycerin patches, however, it is missing the last paragraph of the CLINICAL PHARMACOLOGY (Clinical Trails) section and the last paragraph of the PRECAUTIONS (Drug Interactions) section. These two paragraphs can be found in the insert labeling of Transderm-Nitro manufactured by Ciba-Geigy Corporation permitted 1/26/95 and revised 7/94. The Transderm-Nitro insert labeling is missing the second paragraph from the ADVERSE REACTIONS section which can be found in the Nitro-Dur insert labeling. These issues were previously discussed with Dr. Fenishell (Cardio Renal Drug Division). Dr. Fenishell informed our office that all three paragraphs should be included in generic firms insert labeling regardless if they are based on Nitro-Dur or Transderm-Nitro. Also note that some generic firm's that have based their submission on Transderm-Nitro will not have the same delivery system as Transderm-Nitro [i.e., nitroglycerin in a drug reservoir] but have the same delivery system as Nitro-Dur [i.e., nitroglycerin in the adhesive]. See NOTE TO THE CHEMIST.

-Container label and carton - Primarily Nitro-Dur labels and labeling. Nitro-Dur labels are more current and have updated text. There are minor modifications, which were primarily based on other approved nitroglycerin patch PPI. (This is consistent with the other reviews).

-Patient information insert labeling - Nitro-dur
Note: [See future revision. Transderm-Nitro labeling is most current permitted labeling for nitroglycerin patches, permitted date 5/19/95 and revision date 7/93. Transderm-Nitro has been used as the model for the PPI in the past regardless if the ANDA is based on Nitro-Dur or Transderm-Nitro]. This issue was previously discussed with Jerry Phillips, R.Ph, Chief of the Labeling Branch [and currently Division Director], who was in agreement with this decision.

2. Packaging

    Transderm-Nitro-30s & 100s
    Nitro-Dur-30s
    ANDA-30s

3. The patent [U-158] for Transderm-Nitro (nitroglycerin film transdermal release) is scheduled to expire on 12/4/01.

NOTE: In this submission the firm indicates the following: "... that in our opinion and to the best of our knowledge, no patent information has not been filed claiming the product which is the subject of this application".

4. ANDAs 89-884 (0.2 mg/hr), 89-885 (0.4 mg/hr) and 89-886 (0.6 mg/hr) share a common insert. They must be approved at the same time.

5. We requested the firm delete from their labels and labeling until a decision is made regarding, how generic firms should differentiate between their drug products based on Nitro-Dur and their drug products based on Transderm-Nitro.
[Note both sets of ANDAs have the same delivery system as Nitro-Dur even though the firm has one set of ANDAs based on Nitro-Dur and other set of ANDAs based on Transderm-Nitro].

6. Inactive ingredients:
See NOTES TO THE CHEMIST.

We request the firm to list the imprinting ink used on their patch. The firm has indicated in their response that the imprinting ink contains printing, and that the dried printed ink contains only . [See NOTE TO THE CHEMIST]

7. The following is from a previous NOTE TO THE CHEMIST.

a. Has the firm updated their patent certification statement?

-Chemist/Sema response [from ANDA 89884]: it will be handled by Peter Rickman branch.

b. Should silicone or be listed in the DESCRIPTION section as inactive ingredients?
-Chemist/Sema response [from ANDA 89884]: No.

c. In the firm's description of their finished patch [nitroglycerin transdermal system], they mention that the patch has "printed text" without identifying what the text reads. Can you inform me where the firm indicates what the "printed text" reads in the application?
-Chemist/Sema response [from ANDA 89884] : See batch records. See pages 219, 224, 276, Vol. 5.1 see page 300, Vol. 4.1 stability records.

d. There are two innovators for this drug product Nitro-Dur and Transderm-Nitro. Nitro-Dur's patches contain nitroglycerin in an acrylic-based polymer adhesive and Transderm-Nitro's patches contain nitroglycerin in a drug reservoir, followed by a semipermeable membrane

and then adhesive. This firm has two sets of ANDA's for nitroglycerin transdermal system, one based on Nitro-Dur and the other based on Transderm-Nitro. However, both sets of ANDA's actually have the same delivery system as Nitro-Dur. Is this acceptable, if so please explain?
-Chemist/Sema response [from ANDA 89884]: Accepted to filing Bio. Office. It is acceptable as long as they have the same release rate.

e. The two sets of ANDAs also have the same release rate but differ in size [cm²]. Is this acceptable, if so please explain?
-Chemist/Sema response [from ANDA 89884]: Yes, acceptable.

Date of Review: **7-13-98** Dates of Submission: **6-26-98 and 7-9-98**

Primary Reviewer: Adolph Vezza /S/ Date: 7/16/98

Team Leader: Charlie Hoppes /S/ Date: 7/16/98

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cc: ANDA 89-884 (0.2 mg/hr)
89-885 (0.4 mg/hr)
89-886 (0.6 mg/hr)

Dup/Division
HFD-613/AVezza/CHoppes (no cc:)

DATE: February 25, 1998 Time: 11:00 HFD-650, MPN-II

Subject: Hercon Labs; Nitroglycerin Transdermal Systems, ANDA 89-884, -885, -886

Meeting Type: Teleconference

Meeting Chair: Gordon Johnston

FDA Participants:
Doug Sporn, Director, OGD
Gordon Johnston, Deputy Director, OGD
Mary Fanning, Associate Director Medical Affairs
Dale Conner, Director, Division of Bioequivalence
Lizzie Sanchez, Project Manager, DBE

Hercon Participants:
Robert Pilson
Thomas Atkins
Donald Kauffman, VP, Operations

Meeting Objective: Discuss the skin irritation studies conducted by Mylan for their approved application for Nitroglycerin Patches.

Discussions:

1. Mylan's skin irritation studies which are approved, are an "outlier" as far as these types of studies are concerned. Mylan submitted a single dose irritation study comparing test versus reference. The patches were removed after 12 hours, and readings were done after 30 minutes and 1 hour, in 115 patients. This was followed by a challenge study conducted in 102 patients, where the test product was compared to a known irritant (0.1% SLS). Application was performed on M, W, F for 3 weeks, then there was a rest for 10-17 days and reapplication for 24 hours. Readings were done 24 and 48 hours after removal. Hercon's studies do not match Mylan's, since there is no comparison of test vs. reference.

2. Gordon Johnston explained the history behind skin irritation studies for transdermal products. Over the past three years, since Dr. Wilkin, Director, Division of Dermatologic Products, joined the agency, there has been a coordinated effort to establish standard skin irritation testing for transdermal products. Prior to that the Center did not have extensive experience in this area. Since Dr. Fanning joined OGD, she has been working with Dr. Wilkin to provide consistency in this area. The study design has evolved during the last year

and a half. Inconsistencies were noted in the reviews of these studies, mainly because different reviewers were reviewing these studies unaware of the others recommendations.

3. The Office can not comment on studies on other applications that are currently under review. Only approved applications can be discussed. The only Nitroglycerin ANDA approved are Mylan's, who did not submit a study that meets current standards. However, Nicotine Patches have been approved, where adequate skin irritation studies were submitted.

4. After consulting with several CRO's, Hercon has some medical and safety concerns on the nitroglycerin dosing. However, Hercon needs to do some more research with CRO's to be able to outline these issues. They will submit a fax with all their questions to the attention of Doug Sporn next week. Expedited review of this skin irritation study will be granted.

5. Dr. Fanning stated that skin irritation studies may be conducted on the lower strength of the patch that is intended to be marketed, due to safety concerns.

6. Doug Sporn clarified that even though there has been some inconsistencies in the design of the skin irritation studies, the study submitted by Hercon, which compares test vs placebo has never been acceptable to the Office. Mylan did submit a study that does not meet current standards, however, the firm did compare test vs reference, in addition to the challenge study which compares the test product to 0.1% SLS, a known irritation. Therefore, Hercon is not being treated unfairly by OGD's request that a new study using the current standard (i.e., test vs reference) be conducted.

Agreements:

1. Hercon will submit a fax next week to address safety concerns voiced by several CRO's contacted by Hercon.

2. OGD will be willing to discuss their questions in another teleconference after their questions are reviewed by Dr. Fanning.

Action Items:

1. Provide guidance to Hercon on study design when fax is received by the Office.

Drafted ALS 2/25/98

DATE: February 11, 1998 Time: 11:00 HFD-650, MPN-II

Subject: Hercon Labs, Nitroglycerin Transdermal Systems,
ANDA 89-884, -885, -886
ANDA 89-516, 88-782, 88-783

Meeting Type: Internal Meeting

Meeting Chair: Doug Sporn

FDA Participants:
Gordon Johnston, Deputy Director, OGD
Mary Fanning, Associate Director Medical Affairs
Dale Conner, Director, Division of Bioequivalence
Rabindra Patnaik, Deputy Director, DBE
Lizzie Sanchez, Project Manager, DBE

Meeting Objective: Discuss the status of the above referenced applications regarding skin irritation studies

Discussions:

1. The first submission of April 27, 1993 was reviewed by YC Huang, where a skin irritation study was conducted. The study consisted of an induction phase (3 weeks), followed by a resting period of 2 weeks, and a challenge phase (1 week). The induction phase compared a test article and placebo. No comparison to the reference product was made. After 2 weeks, the challenge phase was done by either comparing the test vs placebo or the innovator and placebo.

2. Our comments regarding these irritation studies on a letter sent on Aug 18, 1994 state:

   a. For the induction study, it is not clear whether the scores reported were mean values. If those were mean values, the firm should be advised to report the mean, range and coefficient of variation of the data. Please clarify.

   b. There was a discrepancy in the number of data set reported in the challenge phase. the firm was asked to clarify why N for the 48-hour score is more than that for the 24 hr score.

   c. The bioequivalence study was conducted on the 0.4 mg/hr patch, while the wear and repeated insult study was done on the 0.2 mg/hr patch. The firm should be advised that

the observations made on the wear properties and irritation potential of this study pertains only to the 0.2 mg/hr patch and does not establish that the larger patches have acceptable skin irritation characteristics.

3. Hercon responded in their amendment from December 8, 1994 (review by Sikta Pradhan, since YC moved to be a team leader), that they reported only peak scores and not averages to avoid dilution of any potential irritancy effect seen. Descriptive statistics were not provided.

   They stated that the discrepancy noted on the number of data was due to the fact that two subjects did not report for the 24 hr evaluation, but did show up for the 48 hour evaluation.

   Regarding the fact that the skin irritation study did not establish acceptable irritation characteristics, the firm submitted clinical evaluations of irritation from the bioequivalence study where no significant irritation was observed.

4. The review of the amendment dated December 8, 1994, does not address the skin irritation study response and this issue is not brought up in the last review done in May 27, 1997, which addresses the firm's amendments from October 10, 1996 and November 22, 1996.

5. In addition, Hercon has a conditional approval for another set of Nitroglycerin applications, ANDA's
   After reformulating the product, a bioequivalence study was conducted and submitted in November 15, 1994, which was found unacceptable. The firm submitted an amendment on November 15, 1996, with reanalysis of data, which was also found unacceptable (letter dated October 6, 1997). No additional amendments have been submitted. There is a correspondence dated December 22, 1997, notifying the agency of an action brought by Key against Hercon on patent infringement.

Agreements:

1. The skin irritation studies submitted by Hercon on ANDA's 89-884, 89-885 and 89-886 are not acceptable. New studies will need to be submitted.

2. The current formulations is different to the one submitted in 1993 and the patch size has changed. There was no comparative testing between test and reference.

Action Items:

1. Hercon was called and a telecon was arranged. This telecon will take place on February 23, 1998 at 2 p.m. in conference room "A".

2. All transdermal products that have been submitted to OGD but not yet approved are to be identified by L. Sanchez with assistance from others in the Div. of Labeling and Program Support. The list will include both ANDA's that are pending with OGD as well as ANDA's that have been pending with the applicant for no more than two years.

   For each transdermal application identified, the following data will be collected:

   - product name and ANDA number
   - applicant
   - date of submission
   - current status of appl.
   - skin irritation studies--were they included? do they compare the RLD to the applicant's product? Do they generally appear to have been done correctly?
   - BE studies--do they appear to have used the proper methodology.

Drafted ALS 2/11/98

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **89-884 (0.2 mg/hr)** Date of Submission: **November 3, 1997**
89-885 (0.4 mg/hr)
89-886 (0.6 mg/hr)

Applicant's Name: **Hercon Laboratories Inc.**

Established Name: **Nitroglycerin Transdermal System**

Labeling Deficiencies:

1. GENERAL COMMENT

   Replace the statement with the symbol "℞ only" or "Rx only" throughout your labels and labeling. We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site: **http:///www.fda.gov/cder/guidance/index.htm** for guidance.

2. IMMEDIATE PATCH

   Satisfactory in draft as of December 8, 1994 submission.

3. CONTAINER (Pouch)

   ANDA 89-886 only - Patient Instruction # 6

   ... the remaining piece ... (rather than ... "the other piece ..."

4. CARTON

   ANDA 89-884 only - see comment under CONTAINER.

   ANDA 89-885 ONLY - Patient Instruction # 4

   Delete the first "and".

5. PROFESSIONAL PACKAGE INSERT LABELING

DESCRIPTION

Add the statement, "The inactive ingredients are: polyester film, silicone and acrylic adhesive with a cross linking agent"., as per our Labeling Deficiencies related to you pursuant to your June 5, 1997 submission.

Please revise your labels and labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

_____

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTES TO THE CHEMIST

1. Do you concur with comments 3(b)(i, ii and iii) under DESCRIPTION? (These are from the previous review.)

   b. DESCRIPTION:

      i. Add the statement, "The inactive ingredients are: polyester film, silicone and acrylic adhesive with a cross linking agent".

      ii. Revise the last paragraph to read as follows:

      Each system contains nitroglycerin in acrylic based polymer adhesive with a cross-linking agent to provide a continuous source of active ingredient. The nitroglycerin transdermal system comprises three layers; 1) the outer backing which is composed of a polyester film and is printed with the name of the drug and strength; 2) nitroglycerin in acrylic-based polymer adhesive; 3) a protective peel strip which covers the second layer and must be removed prior to use. Each system is sealed in a paper polyethylene-foil pouch.

      iii. Diagram

      We encourage you to revise the description of your layers to read as follows:

      OUTER BACKING
      (impermeable)
      SECOND LAYER
      (nitroglycerin in adhesive)
      PROTECTIVE PEEL STRIP
      (release liner)

Chemist/Sema response: Yes

The firm did not make the revision under (i.) above. I asked Sema about it and she said they need to do it so I repeated the comment from the previous review to the firm.

As far as (ii.) goes above the firm has revised as shown below:

The Nitroglycerin Transdermal System comprises 3 layers: 1) a transparent outer backing layer composed of a composite plastic film and is printed with the name of the drug and

strength; 2) nitroglycerin in acrylic-based polymer adhesive with a cross-linking agent; 3) a protective white, translucent peelable liner which covers the second layer and must be removed prior to use. Each system is sealed in a foil-lined pouch.

I spoke to Sema about this and she said that what the firm has is okay.

2. We requested the firm to list the imprinting ink used on their patch 2 reviews ago. The firm indicated in their response that the imprinting ink contains printing, and that the dried printed ink contains only Is this acceptable?

Chemist/Sema response: Yes, if it is not it is not necessary to include inactives, but they still have to provide components of the ink.

I discussed this issue with J. White. She did not ask the firm for this information in the last review (but had in the previous review). Her discussion with UV revealed that UV would not make an issue of this (from a chemistry standpoint) if the firm does not do this and if labeling feels that it is not needed then the firm does not need to do it. Previous discussions between J. White and C. Hoppes were concluded with the decision that since the drug product was not to be taken orally and since the firm has stated that the backing is impermeable, we would not ask the firm for this.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?

Container Labels:

Pouch -

Immediate Patch -

Carton Labeling: (30s)

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Transderm-Nitro

NDA Number: This product is a DESI drug.

NDA Drug Name: Nitroglycerin Transdermal System 0.2 mg/hr.

NDA Firm: Summit Pharmaceuticals (Ciba)

Nitro-Dur® (Schering Corporation) was used as the model to review this application. NDA 20-145/S-009 was approved 2-7-96. The professional insert revision date is 7/95.:

Has this been verified by the MIS system for the NDA? YES

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the container label, carton and patient information insert labeling: Nitro-Dur and/or Trans-Derm Nitro labels and labeling.

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
PROPRIETARY NAME - NONE			
PACKAGING -See applicant's packaging configuration in FTR			

Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	x		
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths? - The firm has committed to color coding in FPL		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			x
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			

Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?			
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?			
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) - *BUT SEE NOTES TO THE CHEMIST	x*		
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			x
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?			
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			x
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			x
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. Label and labeling models:

-Insert labeling - Nitro-Dur® manufactured by Schering-Plough (Key Pharmaceuticals, Inc.), revised 7/95 and approved 2/7/96.
NOTE: Nitro-Dur insert labeling is the most current approved insert labeling for nitroglycerin patches, however, it is missing the last paragraph of the CLINICAL PHARMACOLOGY (Clinical Trails) section and the last paragraph of the PRECAUTIONS (Drug Interactions) section. These two paragraphs can be found in the insert labeling of Transderm-Nitro manufactured by Ciba-Geigy Corporation permitted 1/26/95 and revised 7/94. The Transderm-Nitro insert

labeling is missing the second paragraph from the ADVERSE REACTIONS section which can be found in the Nitro-Dur insert labeling. These issues were previously discussed with Dr. Fenishell (Cardio Renal Drug Division). Dr. Fenishell informed our office that all three paragraphs should be included in generic firms insert labeling regardless if they are based on Nitro-Dur or Transderm-Nitro. Also note that some generic firm's that have based their submission on Transderm-Nitro will not have the same delivery system as Transderm-Nitro [i.e., nitroglycerin in a drug reservoir] but have the same delivery system as Nitro-Dur [i.e., nitroglycerin in the adhesive]. See NOTE TO THE CHEMIST.

-Container label and carton - Primarily Nitro-Dur labels and labeling. Nitro-Dur labels are more current and have updated text. There are minor modifications, which were primarily based on other approved nitroglycerin patch PPI. (This is consistent with the other reviews).

-Patient information insert labeling - Nitro-dur
Note: [See future revision. Transderm-Nitro labeling is most current permitted labeling for nitroglycerin patches, permitted date 5/19/95 and revision date 7/93. Transderm-Nitro has been used as the model for the PPI in the past regardless if the ANDA is based on Nitro-Dur or Transderm-Nitro]. This issue was previously discussed with Jerry Phillips, R.Ph, Chief of the Labeling Branch [and currently Division Director], who was in agreement with this decision.

2. Packaging

    Transderm-Nitro-30s & 100s
    Nitro-Dur-30s
    ANDA-30s

3. The patent [U-158] for Transderm-Nitro (nitroglycerin film transdermal release) is scheduled to expire on 12/4/01.

NOTE: In this submission the firm indicates the following: "... that in our opinion and to the best of our knowledge, no patent information has not been filed claiming the product which is the subject of this application".

4. ANDAs 89-884 (0.2 mg/hr), 89-885 (0.4 mg/hr) and 89-886 (0.6 mg/hr) share a common insert. They must be approved at the same time.

5. We requested the firm delete "TN" from their labels and labeling until a decision is made regarding, how generic firms should differentiate between their drug products based

on Nitro-Dur and their drug products based on Transderm-Nitro.
[Note both sets of ANDAs have the same delivery system as Nitro-Dur even though the firm has one set of ANDAs based on Nitro-Dur and other set of ANDAs based on Transderm-Nitro].

6. Inactive ingredients:
See NOTES TO THE CHEMIST.

We request the firm to list the imprinting ink used on their patch. The firm has indicated in their response that the imprinting ink contains printing, and that the dried printed ink contains only
[See NOTE TO THE CHEMIST]

7. The following is from the previous NOTE TO THE CHEMIST.

a. Has the firm updated their patent certification statement?

-Chemist/Sema response [from ANDA 89884]: it will be handled by Peter Rickman branch.

b. Should silicone or be listed in the DESCRIPTION section as inactive ingredients?
-Chemist/Sema response [from ANDA 89884]: No.

c. In the firm's description of their finished patch [nitroglycerin transdermal system], they mention that the patch has "printed text" without identifying what the text reads. Can you inform me where the firm indicates what the "printed text" reads in the application?
-Chemist/Sema response [from ANDA 89884] : See batch records. See pages 219, 224, 276, Vol. 5.1 see page 300, Vol. 4.1 stability records.

d. There are two innovators for this drug product Nitro-Dur and Transderm-Nitro. Nitro-Dur's patches contain nitroglycerin in an acrylic-based polymer adhesive and Transderm-Nitro's patches contain nitroglycerin in a drug reservoir, followed by a semipermeable membrane and then adhesive. This firm has two sets of ANDA's for nitroglycerin transdermal system, one based on Nitro-Dur and the other based on Transderm-Nitro. However, both sets of ANDA's actually have the same delivery system as Nitro-Dur. Is this acceptable, if so please explain?
-Chemist/Sema response [from ANDA 89884]: Accepted to

filing Bio. Office. It is acceptable as long as they have the same release rate.

e. The two sets of ANDAs also have the same release rate but differ in size [cm²]. Is this acceptable, if so please explain?
-Chemist/Sema response [from ANDA 89884]: Yes, acceptable.

Date of Review: 2-17-98 Date of Submission: 11-3-97

Primary Reviewer: Adolph Vezza /S/ Date: 3/25/98

Team Leader: Charlie Hoppes /S/ Date: 3/25/98

cc: ANDA 89-884 (0.2 mg/hr)
89-885 (0.4 mg/hr)
89-886 (0.6 mg/hr)

Dup/Division
HFD-613/AVezza/CHoppes (no cc:)

review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 89-884 (0.2 mg/hr)
89-885 (0.4 mg/hr)
89-886 (0.6 mg/hr)

Date of Submission: June 5, 1997

Applicant's Name: Hercon Laboratories Inc.

Established Name: Nitroglycerin Transdermal System

Labeling Deficiencies:

1. CONTAINER (Pouch)

   a. We encourage you to differentiate the different strengths of container labels by using contrasting colors and/or boxing.

   b. Relocate the established name, to appear at the top of the front panel prior to the rate of release and the size of the system.

   c. Print "*in vivo*" in lowercase italic print.

   d. Each system ___ cm^2 contains ___ mg of nitroglycerin in acrylic-based polymer adhesive with a cross-linking agent.

   e. Patient Instructions

      i. To be consistent with your Patient Package Insert revise patient instruction #4 to read as follows:

         Hold patch by the smaller part of the backing (which is still in place) to avoid touching the sticky side of the patch. Apply the sticky side of the patch to your skin. Smooth down.

      ii. If space permits revise patient instruction #6 to be consistent with your Patient Package Insert, "... in place. Then wash your hands with soap and water to remove any drug residue".

iii. Add the statement "APPLY IMMEDIATELY UPON REMOVAL FROM POUCH", at the end of patient instruction #6.

iv. We encourage you to add the statement "Usual Dosage: Each 24 hour period should include a patch-on period of 12 to 14 hours, followed by a patch-free interval; unless otherwise directed by your physician", following patient instruction #6.

v. If space permits, add the storage recommendation statement.

2. Carton

a. Revise the "Usual Dosage" statement to read as instructed in comment 1(e)(iv).

b. Please refer to comments 1(a, c, d and e) under CONTAINER.

3. Professional Package Insert Labeling:

a. General Comment:

Use consistent format when referring to section headings in the text of the insert (i.e., see **CLINICAL PHARMACOLOGY**).

b. DESCRIPTION:

i. Add the statement, "The inactive ingredients are: polyester film, silicone and acrylic adhesive with a cross linking agent".

ii. Revise the last paragraph to read as follows:

Each system contains nitroglycerin in acrylic based polymer adhesive with a cross-linking agent to provide a continuous source of active ingredient. The nitroglycerin transdermal system comprises three layers; 1) the outer backing which is composed of a polyester film and is printed with the name of the drug and strength; 2) nitroglycerin in acrylic-based polymer adhesive; 3) a protective peel strip which covers the second layer and must be removed prior to use. Each system is sealed in a paper polyethylene-foil pouch.

iii. Diagram

We encourage you to revise the description of your layers to read as follows:

OUTER BACKING
(impermeable)
SECOND LAYER
(nitroglycerin in adhesive)
PROTECTIVE PEEL STRIP
(release liner)

c. Information for the Patient.

i. When describing the backing/protective liner, use a phrase such as "... it has translucent white backing with a peelable liner divided into two strips ..." instead of "prescored".

ii. We encourage you to add the "Usual Dosage: Each 24 hour ..." statement, following the text under "Important".

d. HOW SUPPLIED

Add the text, "clear white backing" to the physical description of system.

4. PATIENT PACKAGE INSERT

Please refer to our comment 3(c) under Information for the Patient.

Please revise your labels and labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approva

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

MAY 7 1997

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 89-886

Date of Submission: October 10, 1996

Applicant's Name: Hercon Laboratories Inc.

Established Name: Nitroglycerin Transdermal System 0.6 mg/hr

Labeling Deficiencies:

1. General Comment

   Delete "TN" from your labels and labeling.

2. Patient Package Insert Labeling:

   Revise your patient package insert labeling to be in accord with the enclosed approved patient package insert labeling of Transderm-Nitro (nitroglycerin) Transdermal System [Approved 5/19/94 and revised 7/93]. Please note, minor modifications may be required due to drug product differences.

3. Professional Package Insert Labeling:

   a. DESCRIPTION:

      List the imprinting ink which is used on the patch, as requested in our letter dated March 29, 1996.

   b. HOW SUPPLIED:

      Revise "and the strength in mg/hr" to read "and the release rate in mg/hr".

   c. See comment under Patient Package Insert and revise the information reprinted at the end of your insert accordingly. In addition, we note you have revised the fifth pictorial patient instruction, which differs from your last submitted insert labeling, as well as your patient package insert labeling. The intended patient instruction to be conveyed from this picture is unclear. Please revise and/or comment.

Please revise your labels and labeling, as instructed above, and submit in draft.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: Transderm-Nitro (nitroglycerin) Transdermal System patient package insert

How to use Transderm-Nitro®

nitroglycerin Transdermal Therapeutic System for the prevention of angina

Transderm-Nitro is easy to use — it has a clear plastic backing, and a special adhesive that keeps the system firmly in place.

Where to place Transderm-Nitro

Select any area of skin on the body, EXCEPT the extremities below the knee or elbow. The chest is the preferred site. The area should be clean, dry, and hairless. If hair is likely to interfere with system adhesion or removal, it can be clipped but not shaved. Take care to avoid areas with cuts or irritations. Do NOT apply the system immediately after showering or bathing. It is best to wait until you are certain the skin is completely dry.

How to apply Transderm-Nitro® (Nitroglycerin)

1. Each Transderm-Nitro system is individually sealed in a protective pouch. Tear open this pouch at the indicated indentations. Carefully pick up the system lengthwise with the tab up, and the clear plastic backing facing you. You should be able to see the white cream containing nitroglycerin. (On very rare occasions, you may find a system without any white medication in it. Do not use it. Simply apply another system.)

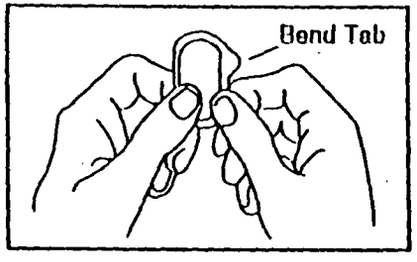

Figure A

2. Firmly bend the tab <u>forward</u> with the thumb (Figure A). With both thumbs, begin to remove the <u>clear plastic</u> backing from the system at the tab (Figure B). Do not touch the inside of the exposed system, because the adhesive covers the entire surface.

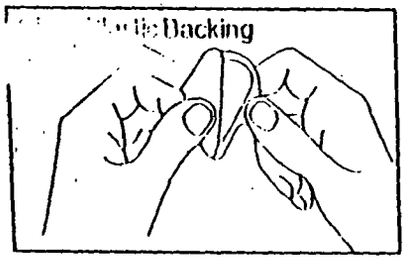

Figure B

3. Continue to remove the <u>clear plastic</u> backing <u>slowly</u> along the length of the system, allowing the system to rest on the outside of your fingers (Figure C).

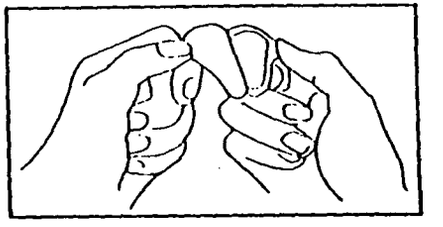

Figure C

4. Place the exposed, adhesive side of the system on the chosen skin site. <u>Press firmly</u> in place with the palm of your hand (Figure D). Once the system is in place, do not test the adhesion by pulling on it.

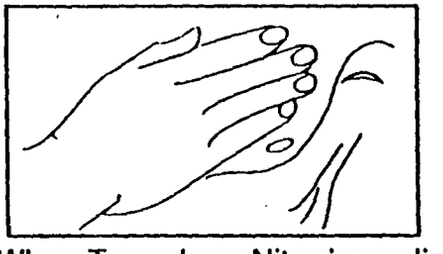

Figure D

When Transderm-Nitro is applied to your body, the nitroglycerin contained in the system begins to flow onto your skin through a unique rate-controlling membrane. This membrane allows the nitroglycerin to be released and available for absorption through your skin at a uniform rate.

5. At the time recommended by your doctor, remove and discard the system.

6. Place a new system on a different skin site, following steps 1-4, according to your doctor's instructions.

Please note!

Contact with water, as in bathing, swimming, or showering will not affect the system. In the unlikely event that a system falls off, discard it and put on a new one on a different skin site.

Precautions

The most common side effect is headache, which often decreases as therapy is continued, but may require treatment with a mild analgesic. Although uncommon, faintness, flushing, and dizziness may occur, especially when suddenly rising from the recumbent (lying horizontal) position. If these symptoms occur, remove the system and notify your physician.

Skin irritation may occur. If it persists, consult your physician.

Keep these systems and all drugs out of the reach of children.

Important

Your doctor may decide to increase or decrease the size of the system, or prescribe a combination of systems, to suit your particular needs. The dose may vary depending on your individual response to the system.

This system is to be used for preventing angina, not for treating an acute attack.

DO NOT STORE ABOVE 86°F (30°C).

Do not store unpouched. Apply immediately upon removal from the protective pouch.

666592 Printed in U.S.A. C93-19 (Rev. 7/93)

Summit Pharmaceuticals

Dist. by:
Summit Pharmaceuticals
Ciba-Geigy Corporation
Summit, New Jersey 07901

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

Date of Review: 3-1-96 **Date of Submission: 8-7-95**

Primary Reviewer: Adolph Vezza

Secondary Reviewer:

ANDA Number: 89-886 **Review Cycle: Fourth**

Applicant's Name [as seen on 356(h)]: Hercon Laboratories Inc.

Manufacturer's Name (If different than applicant):

Proprietary Name:

Established Name: Nitroglycerin Transdermal System 0.6 mg/hr

LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE CHEMISTRY COMMENTS TO THE FIRM:

[NOTE: These deficiencies can be located on the x-drive as detailed in notes from Ted Sherwood regarding the New X-Drive]

A. CHEMISTRY DEFICIENCIES

B. LABELING DEFICIENCIES

Container Labels:

Pouch - Satisfactory as of 8-7-95 submission.

Immediate Patch - Satisfactory as of 12-8-94 submission.

Carton Labeling: (30s)

Satisfactory as of 8-7-95 submission.

Professional Package Insert Labeling:

1. DESCRIPTION

a. Revise the last sentence of the third paragraph to read: ...delivered approximately 7% of...

b. List the imprinting ink which is used on the patch.

2. **PRECAUTIONS**

a. Carcinogenesis, Mutagenesis, Impairment of Fertility.

i. Delete the from the subsection title.

ii. Delete the penultimate sentence of the second paragraph (Incidences...females).

b. Revise the subsection title as follows:

Pregnancy: Pregnancy Category C:

Patient Package Insert Labeling:

Satisfactory as of 8-7-95 submission.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels:

Pouch - Satisfactory as of 8-7-95 submission.

Immediate Patch - Satisfactory as of 12-8-94 submission.

Carton Labeling: (30s)

Satisfactory as of 8-7-95 submission.

Professional Package Insert Labeling:

Not Satisfactory. (See comments above)

Patient Package Insert Labeling:

Satisfactory as of 8-7-95 submission.

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Transderm-Nitro

NDA Number: This product is a DESI drug.

NDA Drug Name: Nitroglycerin Transdermal System 0.2 mg/hr.

NDA Firm: Summit Pharmaceuticals (Ciba)

Nitro-Dur® (Schering Corporation) was used as the model to review this application. NDA 20-145/S-009 was approved 2-7-96. The professional insert revision date is 7/95.:

Has this been verified by the MIS system for the NDA? YES

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the container label, carton and patient information insert labeling: Nitro-Dur and/or Trans-Derm Nitro labels and labeling.

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
PROPRIETARY NAME			X
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	

If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	x		
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths? see FOR THE RECORD	?	?	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?	X		
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			x
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?			
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?			
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?			

Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)	x		
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			x
Does USP have labeling recommendations? If any, does ANDA meet them?			
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	x x		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			x
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			x
Insert labeling references a food effect or a no-effect? If so, was a food study done?			x
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. Hercon has changed the description of this product in the DESCRIPTION section of the professional insert from a "laminated matrix" to "crosslinked acrylic-based polymer adhesive". Is this accurate? **YES**

2. Is there a "reservoir" in this product as the company claims? **NO**

3. In their depiction of the cross section of this product the company has revised the middle layer from "Adhesive Reservoir" to "Adhesive Matrix". Is this accurate? **YES**

4. I note comment 3 under "LABELING" in your third chemistry review. The firm has changed the first sentence of the last paragraph of the DESCRIPTION section from

to The Nitroglycerin Transdermal System contains nitroglycerin in a cross-linked acrylic-based polymer adhesive to provide a continuous source of active ingredient." Is this change satisfactory or is the following more

acceptable? ...in a cross-linked polymer adhesive

to provide... **The new statement is acceptable.**

5. **I spoke to two chemists about the above issues:**

John Simmons
- **"cross-linked acrylic based polymer adhesive" should be sufficient.**

Glen Smith - Various Issues
- **The inactives are food-grade but what if somewhere down the road a different firm uses different inactives and thus they may use something that could possibly be allergenic?**
- **If Hercon has not mentioned the inactives by name in the application we can ask them to do so. They may choose not to claiming that it is a trade secret.**
- **Hercon may consider the components of their "cross linked acrylic-based polymer adhesive" to be proprietary information thus "cross linked acrylic-based polymer adhesive" = "other ingredients".**

Sema also believes that the statement is fine as is. Since the firm did not voluntarily provide the actual components of the acrylic-based polymer adhesive they may be considered proprietary.

6. Is there a discrepancy between the DESCRIPTION section of the insert and the composition statement? **NO**

7. Does the imprinting ink used on patch to designate the amount of drug delivered per hour considered part of the "inactive ingredients"? **YES. There is a possibility that the ink may permeate the backing of the product.**

8. Please explain to me how ANDAs 89-884 (0.2 mg/hr), 89-885 (0.4 mg/hr) and 89-886 (0.6 mg/hr) can have the same rate of release and the same cross-linked acrylic-based polymer adhesive as ANDAs

yet have a patch size which is different. **The amount of NTG released per unit area is different for the two products because of differences in the cross-linked acrylic-based polymer adhesive..**

9. **Please note that Sema's answers are bolded and follow the questions.**

FOR THE RECORD:

1. Nitro-Dur® manufactured by Schering-Plough (Key Pharmaceuticals, Inc.), revised 7/95 and approved 2/7/96, was used for package insert labeling model.

2. The drug product will be marketed in cartons of 30 as is the reference listed drug.

3. This drug product is not listed in the USP or the PF.

4. There is an active patent for Nitro-Dur's delivery system. This drug product's delivery system is similar.

5. The above "NOTES/QUESTIONS TO THE CHEMIST" are to be considered part of the record.

6. ANDAs 89-884 (0.2 mg/hr), 89-885 (0.4 mg/hr) and 89-886 (0.6 mg/hr) share a common insert. They must be approved together.

7. The firm feels that they have adequately distinguished the three strengths for this product by the fact that each strength is a different size. Further, they believe that since the name of this drug product is printed in italics on the cartons and on the individual pouches for ANDAs 89-884 (0.2 mg/hr), 89-885 (0.4 mg/hr) and 89-886 (0.6 mg/hr) that this fact would distinguish them from their virtually identical and already approved Nitroglycerin Transdermal Systems ANDAs
   which do not have the drug product name printed in italics. The only difference between these 2 sets of ANDAs is that the latter ones are smaller in size. (Please see comment 8 and the answer under NOTES/QUESTIONS TO THE CHEMIST).

8. The bio is still pending on this application.

/S/ 3/1/96

Primary Reviewer — Date

/S/ 3-4-96

Acting Team Leader
Labeling Review Branch — Date

cc:
ANDA 89-886
DUP/DIVISION FILE

FILE

Tele-minutes

2/2/96

From: J. Gross

RE: Hercon
NTG-TDS
ANDAs 89-884, 89-885, [redacted]
BIO 96-018

Firm contact: Joe Sobecki (717) 764-1191

Background:
In a letter dated 11/30/95 the firm was advised that the submitted study failed to satisfy the current BE-criteria and options for study analysis were given. The firm has reviewed our concerns and in a letter from them dated 1/29/96, they request a meeting to discuss issues related to the reanalysis of the data.

Action Plan:
The issues were discussed with the primary reviewer S. Pradhan and Dr. Chan and it was decided that in lieu of a meeting it would be better for the firm to submit the reanalysis of their data for our review. The firm would be called an notified that the data should be submitted for review.

Action:
The firm was called and advised that rather than granting a meeting we would like the data submitted for review. The firm was insistent on a meeting since they wanted more feed back on their proposed statistical model. Dr. Chan was again consulted during the phone call about this issue. He suggested that the firm submit the data and we would review it and offer suggestions as soon as it is received rather than placing it in the review queue. This exception would only be granted for the statistical data. The other deficiencies contained in the 11/30/95 OGD correspondence would be subject to the normal review cycle. The firm agreed and the call was ended.

Agency Action:

1. Document may be closed
2. The firm will submit the statistical analysis to Bio 96-018 for review and comments. The other deficiencies will be submitted to the application.
3. Bio 96-018 may be closed.

This Review supersedes that of May 6, 1993

REVIEW OF PROFESSIONAL LABELING

ANDA - Amendment

DRAFT

DATE OF REVIEW: October 15, 1993

ANDA #: 89-884 (0.2 mg/hr)
89-885 (0.4 mg/hr)
89-886 (0.6 mg/hr)

NAME OF FIRM: Hercon Laboratories Corporation

NAME OF DRUG: Generic: Nitroglycerin Transdermal System

DATE OF SUBMISSION: April 27, 1993 (received April 28, 1993)

COMMENTS:

General Comments:

1. We note that when the different strengths are compared side to side they are barely discernible. This issue concerns us. We believe these products could easily be confused and could lead to dispensing errors. Please comment on how you are going to differentiate your products.

2. We refer you to 21 CFR 314.94(a)(8)(ii) which clearly defines the quantities of draft or final printed labeling to be submitted.

Individual Patch: Satisfactory in draft.

Foil Pouch:

We ask that you include a revision date or other identifying mark.

Carton: 30 count

1. Federal caution statement, ...DISPENSING WITHOUT PRESCRIPTION. (please delete).

2. We ask that you include a revision date or other identifying mark.

Patient Package Insert:

Please revise your patient package insert to be in accord with the patient package insert of Transderm-Nitro by Ciba revised

6/89 and approved December 1, 1989, then submit draft copy.

Insert:

DESCRIPTION

In accordance with good pharmaceutical practice, all dosage forms should be labeled to state all inactive ingredients (refer to USP General Chapter <1091> for guidance). We believe this is an important public health measure. Please respond by noting the inactive ingredients present in these products. This can be done in an "Each system contains:..." statement.

INDICATIONS AND USAGE

This entire section should be revised to be in accord with the *Federal Register* notice of July 15, 1993 as follows:

> Transdermal nitroglycerin is indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute attack.

ADVERSE REACTIONS

1. Paragraph 2, ...and treatment see **OVERDOSAGE.** (please note that **"OVERDOSAGE"** should be in bold capitalized print).

2. Please include the following as a new paragraph between current paragraph 4 and 5:

> Application-site irritation may occur but is rarely severe.

OVERDOSAGE

Last paragraph, ...blue, 1 to 2 mg/kg... (note "to" rather than a hyphen).

DOSAGE AND ADMINISTRATION

Paragraph 1, penultimate sentence, ...is sufficient (see **CLINICAL PHARMACOLOGY**). (note: **"CLINICAL PHARMACOLOGY"** should be in bold capitalized print).

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their labels and labeling, then prepare and submit draft copy for our review and comment.

TO THE CHEMIST:

1. Please confirm the amount of nitroglycerin and the delivery rate as found in the DESCRIPTION section.

   - 0.027 mg of nitroglycerin per hour
   - 7.5, 15 and 22.5 cm^2 products deliver approx 0.2, 0.4 and 0.6 mg of nitroglycerin per hour
   - after 12 hours, 6% of original contents has been delivered
   - 7.5, 15 and 22.5 cm^2 systems contain 40, 80 and 120 mg of nitroglycerin respectively

2. The firm has included a cross section of the system in the HOW SUPPLIED section. Is this figure correct?

FOR THE RECORD:

1. Labeling model, division guidance of July 28, 1989, plus several edits. In addition the patient package insert is to be in accord with Ciba's Transderm Nitro (listed drug for Hercon's product). Please note that the foil pouch and carton are more in line with Nitro-Dur (this is satisfactory).

2. Storage

   Transderm-Nitro: Do not store above 86°F

   Hercon: Store at controlled room temperature 15° - 30°C (59° - 86°F)

   Nitro-Dur: Store at controlled room temperature 15°-30°C. (59°-86°F). Do not refrigerate.

   Note: Hercon's storage recommendation is satisfactory. We have several products at CRT.

3. No dispensing recommendations.

4. This is not a USP product.

5. The carton will container 30 systems per box.

6. The product is completely reformulated. The firm stated that this response makes all previously submitted material moot.

7. Please note that Hercon has 2
   (

8. The firm has done a new bio study.

9. Please note that delivery rates and amounts differ from product to product. The generic firm states what is accurate for their product and we confirm this information (see comment to chemist). This is based on conversations with T. Poux former primary reviewer.

John Grace

cc: HFD-638/JGrace/JPhillips (no cc:)
mpd/10/20/93/89884oct.93
Review
Final

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 5/24/93

NDA NUMBER: 89-884 0.2 mg/hr; 89-885 0.4 mg/hr; 89-886 0.6 mg/hr

IND NUMBER:

TELECON/MEETING

INITIATED BY: ☒ APPLICANT/SPONSOR ☐ FDA

MADE: ☐ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: Nitroglycerin Transdermal System

FIRM NAME: Hercon

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Joseph J. Sobecki, RAC

TELEPHONE NO.: 717-764-1191

Major amendments were received for the referenced applications. Hercon currently has conditionally approved applications for nitroglycerin transdermal system 0.2 mg/hr, 0.4 mg/hr & 0.6 mg/hr (88-782, 89-516, 88-783). Joseph Sobecki was contacted regarding the pending applications. He stated that these applications contain a different formulation from that of the previous conditionally approved applications.

SIGNATURE: /S/ CBD

DIVISION: HFD-632

FORM FD 2587 (11/77)

PBS, OGD

ORIGINAL IND/NDA

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 19 AUG 92

NDA NUMBER: 89-933, 89-934,

IND NUMBER: 89-886 1
89-884, 89-885

TELECON/MEETING

INITIATED BY
- ☐ APPLICANT/SPONSOR
- ☒ FDA

MADE
- ☐ BY TELEPHONE
- ☐ IN PERSON

PRODUCT NAME: nitroglycerin

FIRM NAME: Hercon

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Joe Solecki

TELEPHONE NO.: 717-764 1191

Inquiry was made to the firm on their interest to pursue these applications. NA letters were issued in 1988.

The firm will pursue, letters will be sent to the files.

SIGNATURE: (S)

DIVISION: 06D

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

[redacted] OF PROFESSIONAL LABELING

[redacted] Amendment

DRAFT

DATE OF REVIEW: [redacted]

NDA #: 89-886 (5 mg/24 hr)
89-886 (10 mg/24 hr)
89-886 (15 mg/24 hr) NAME OF FIRM: [redacted]

NAME OF DRUG: Trade: Transdermal Nitroglycerin System
Generic: Nitroglycerin Transdermal System

DATE OF SUBMISSION: May 11, 1988

COMMENTS:

Individual patch (Direct patch and adhesive backing):

Direct patch (protective covering): Satisfactory, however the firm may wish to consider our letter of May 18, 1988. We are concerned about the amount of information you propose to display in a small area.

Adhesive backing Label: Delete the letter "s" in 24 hrs, otherwise satisfactory.

Carton: Satisfactory

Patient Package Insert: Satisfactory

Professional Insert: Replace the words "1 hour" with "one hour" in sentence two, paragraph two of the CLINICAL PHARMACOLOGY section.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm submit final printed labels.

/S/

Dr. Bacsanyi

cc:
HFD-238
JBacsanyi/je/5-31-88
rpl
7856A/ pg 7

REVIEW OF PROFESSIONAL LABELING

ANDA/Orig. Amendment/DRAFT

DATE OF REVIEW: March 25, 1988

ANDA: 89-884 (5 mg/24 hour) NAME OF FIRM: Hercon Laboratories Corporation
89-885 (10 mg/24 hour)
89-886 (15 mg/24 hour)

NAME OF DRUG: Trade: Transdermal Nitroglycerin System
Generic: Nitroglycerin Transdermal System

DATE OF SUBMISSION: March 11, 1988

COMMENTS:

Individual patch (direct patch and adhesive backing)

Direct patch (protective covering): delete the word "Nitroglycerin".
Adhesive backing label: Add the word "transdermal" after nitroglycerin.
You may shorten the address to create additional space if necessary.

Carton

See 89-884. BH 4/20/88

Chemist: Please check the list of inactive ingredients. Otherwise it is satisfactory.

Patent package insert

In the "Some Special Advice" section please make a comment whether patch can be worn in the bath, in shower or while swimming etc.

Insert - professional

Chemist: Please check for adequacy of listed inactive ingredients.
Delete the decimal point from 125 mg in the DESCRIPTION section.

In the CLINICAL PHARMACOLOGY section:
Replace the word "result" with "resultant" in paragraph one. Will check with bio about the blood levels in the bio-study.

The INDICATIONS section should be boxed.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their individual patch, carton and insert labeling, then prepare and submit draft labeling for our review and comment.

/S/
Janos Bacsanyi

cc:
HFN-238
JBacsanyi/trc/4/6/88
2189m page 22
Review of Prof. Labeling

6.1

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 02-Nov-1998 01:49pm EST
From: Pat Beers-Block
BEERSBLOCKP
Dept: HFD-320 MPN1 273
Tel No: 301-594-0093 FAX 301-594-2202

TO: Russell Livermore (LIVERMORER)
TO: Eda Howard * (HOWARDE)

CC: Timothy Ames (AMEST)
CC: Robert West (WESTR)
CC: Gordon Johnston (JOHNSTONG)
CC: Jonathan Cook (COOKJ)
CC: Doug Sporn (SPORND)

Subject: COMIS Data changes for ANDAs 89-884/5/6

Russ and Eda,

ANDAs #89884, 89885 and 89886 were originally submitted to the Agency on Nov 16, 1987 based on a federal register notice for nitroglycerin transdermal systems, and accepted by the Agency as fileable at that time. However, in 1992 our regulations changed such that all ANDAs had to be compared with a reference listed drug, and they could not be filed based solely on a Federal Register notice.

It was not until the firm submitted their October 10, 1996 amendments for these ANDAs that provided for product reformulation and that included information about the bioequivalence of Hercon's ANDAs with a RLD that these applications were considered "acceptable" for filing. All previous submissions would, by today's procedures, have been considered unacceptable and a refuse to file entry would have been used in COMIS to reflect the status of each submission received prior to the firm's submission of an appropriate comparative biostudy.

It is for this reason that we now request that all COMIS entries for ANDAS #89-884/5/6 from the time period of November 16, 1987 until October 10, 1996 be modified to contain the decision code of RF (refuse to file). By so doing, COMIS will reflect the unacceptable nature of these ANDAs until the firm had a legal RLD with which to compare their product.

Thank you for your help. If you have any questions, please feel free to contact me. pb2

6.1

FILE

E L E C T R O N I C M A I L M E S S A G E

Date: 30-Nov-1995 07:44am EST
From: Jason Gross
GROSSJ
Dept: HFD-612 MPN2 113
Tel No: 301-594-2290 FAX 301-594-0181

TO: John Simmons (SIMMONSJ)
TO: Sema Basaran (BASARANS)
TO: Timothy Ames (AMEST)
TO: Yih Chain Huang (HUANGY)
TO: Sikta Pradhan (PRADHANS)
TO: Robert West (WESTR)
TO: Mark Anderson (ANDERSONM)

Subject: Fatal Flaw

RE: Hercon
NTG-TDS
89-884, 885, 886

The Bio-study has failed the bio-criterion for approval. The firm may be able to correct but for now the study is not acceptable.

Please note this should not receive minor amendment status.

FYI
JAG

ANDA 84-886

E L E C T R O N I C M A I L M E S S A G E

Date: 02-Feb-1995 10:33am EST
From: Donald Hare
HARE
Dept: HFD-604 MPN2 286
Tel No: 301-594-0337 FAX 301-594-018

TO: William Rickman (RICKMAN)

CC: Doug Sporn (SPORN)
CC: Gordon Johnston (JOHNSTON)
CC: Sharon Sheehan (SHEEHANS)
CC: Mary Ann Holovac (HOLOVACM)
CC: George Scott (SCOTTG)
CC: Gary Buehler (BUEHLER)

Subject: Key's Nitro-Dur

Peter:

As a heads-up; Gordie and I reviewed the " Lipicky to Temple" informational memorandum regarding the approval of Schering-Key's supplement which would grant approval to Nitro-Dur. Schering-Key has submitted a formulation patent which will be listed in the Orange Book at the time of approval. All firms with a pending 505(b)(2) or 505(j) application using the Schering product as the reference drug will have to amend their applications with an appropriate patent certification when the Orange Book displays this formulation patent on the approved Nitro-Dur transdermal patch.

Don

REVIEW OF PROFESSIONAL LABELING

ANDA Orig

DRAFT

DATE OF REVIEW: [redacted], 1987

ANDA #: 89-888 NAME OF FIRM: Marcon

NAME OF DRUG: Trade: NTS 5
Generic: Nitroglycerin Transdermal System, 5 mg

DATE OF SUBMISSION: November 12, 1987

COMMENTS:

General: Numbers are not to be a part of the trade name. Such numbers have been shown to contribute to confusion and dispensing errors. The trade name "NTS" is presently used by Baker, therefore Marcon must select another trade name.

Direct Patch Label * Not Satisfactory

Delete numeral from the brand name. Add the word "transdermal" also the address of the company (city, state, zipcode).

There is no labeling submitted for the adhesive foam pad (which will show when the patch is on the patient).

Carton: "Generic" labeling submitted.

Delete numeral from the brand name - Reverse the Fahrenheit and Celsius designations in the storage directions.

Patient package insert:

X Modeled after the Nitrodisc (Searle) patient package insert. Reverse the Fahrenheit and Celsius designations in the storage recommendations. Add the name and address of the manufacturer, and date of issue to the bottom of the insert.

Profes[redacted]

[redacted] is used as a model -
[redacted]tions should follow the HOW SUPPLIED section. Will [redacted] about the blood levels in the bio-study.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their direct patch, carton and insert labeling and submit draft labeling for the adhesive foam pad, that is, information which will show when the foam pad is on the skin. Final printed labeling cannot be approved until firm selects another trade name.

/S/

Dr. Bacsanyi

cc:
HFN-238
DBacsanyi/je/12-18-87
rpl
7683A/ pg 5-6