CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21134

CHEMISTRY REVIEW(S)
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-134  DATE REVIEWED: 1-27-00
REVIEW #: 1  REVIEWER: J. T. Piechocki

<table>
<thead>
<tr>
<th>SUBMISSION TYPE</th>
<th>DOCUMENT DATE</th>
<th>CDER DATE</th>
<th>ASSIGNED DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORIGINAL</td>
<td>02-06-99</td>
<td>03-06-99</td>
<td>15-06-99</td>
</tr>
<tr>
<td>AMENDMENT</td>
<td>12-08-99</td>
<td>13-08-99</td>
<td>17-08-99</td>
</tr>
</tbody>
</table>

Amendment provide for:
12-08-99  Clarification of location of packaging site.

NAME & ADDRESS OF APPLICANT:
Parke-Davis Pharmaceuticals Limited
P.O. Box 4119
Road 689-KM 1.9
Vega Baja, Puerto Rico 00694-4119

Agent: Parke-Davis Pharmaceutical Research
Attn: Irving G. Martin, Ph.D.
Vice-President, FDA Liaison, Worldwide Regulatory Aff.
Warner-Lambert Company
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, MI 48106-1047
Phone: 734-622-7756
FAX: 734-622-3823

DRUG PRODUCT NAME
Proprietary: Nitrostat®
Established: Propanetriol trinitrate
Code Name#: CI-782, PD 79964, DNG
Chem Type/Ther Class: 5 S

PHARMACOL. CATEGORY/INDICATION: Anti-anginal pectoris
**DOSAGE FORM:**
Tablet

**STRENGTHS:**
0.3, 0.4 and 0.6 mg/tablet

**ROUTE OF ADMINISTRATION:**
Sublingual

**Rx/OTC:**
- X Rx

**SPECIAL PRODUCTS:**
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

**STRUCTURAL FORMULA:**

\[
\begin{align*}
\text{O}_2\text{NO} & \quad \text{ONO}_2 \\
& \quad \text{ONO}_2
\end{align*}
\]

**CHEMICAL NAME:** 1,2,3-Propanetriol, trinitrate
Nitroglycerin

**MOLECULAR FORMULA:** C,H,N,O

**MOLECULAR WEIGHT:** 227.09

**CAS Number:** 55-63-0

**SUPPORTING DOCUMENTS:**

<table>
<thead>
<tr>
<th>Type/Number</th>
<th>Subject</th>
<th>Holder</th>
<th>Status</th>
<th>Letter Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF</td>
<td>SDM-26, Diluted Nitroglycerin</td>
<td>Adequate, rev. dated 1/18/2000</td>
<td>10/19/95</td>
<td></td>
</tr>
<tr>
<td>DMF</td>
<td>Tin plate metal caps with inner seals</td>
<td>*</td>
<td>4/31/99</td>
<td></td>
</tr>
<tr>
<td>DMF</td>
<td>WP/SOR171</td>
<td>*</td>
<td>4/07/99</td>
<td></td>
</tr>
<tr>
<td>DMF</td>
<td>Coiler</td>
<td>*</td>
<td>4/14/99</td>
<td></td>
</tr>
</tbody>
</table>

* These DMFs have all been reviewed previously and these items were used in the original approved product Nitrostat® which this reformulated product will replace.

**RELATED DOCUMENTS (if applicable): (1,2,3)**
IND: Study of tablet of improved weight control, content uniformity and physical stability.

CONSULTS:
None

REMARKS:
Product has been manufactured for over 5 decades as Nitrostat® but there have been disruptions in the supply to the patients attributable to problems with the friability, weight variation and physical stability of the current product. For this reason reformulation was undertaken and the current formulation developed. (1, 2, 20)

Labeling call for “Storage at Controlled Room Temperature 25⁰-25⁰C (68⁰-77⁰F) [see USP].”

Based upon stability data submitted and the pre-application meeting with the Agency (10-1-99) {B1.2, p. 64, 3.7.6}.

CONCLUSIONS & RECOMMENDATIONS:
It is recommended that this application be approved from a CMC perspective and a 24-month expiration date be granted based upon historical stability data on the old formulation and current stability data on the slightly modified formulation.

Joseph T. Piechocki, Review Chemist

cc:
Org. NDA 21-134
HFD-110/PM
HFD-810/JTPiechocki/
HFD-110/PM
HFD-110/KSrinivasachar
HFD-810/JSimmons (NMEs only)
R/D Init by: KSrinivasachar
MEMORANDUM

Date: December 1, 1999

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

Subject: Labeling and Nomenclature Committee Review

Parke-Davis (a division of Warner Lambert Company) has marketed the nitroglycerin sublingual tablet since before 1938. Nitrostat is a trademark that is registered with the US Patent & Trademark Office (PTO) and identified by No. 954,318. The owner of the trademark, Warner-Lambert Company, first used the trademark in interstate commerce on August 23, 1971. A trademark application was later filed with the PTO on December 8, 1971 seeking placement of the trademark on the Federal Trademark Register. The PTO issued the registration of the Nitrostat trademark on March 6, 1973.

Parke-Davis has submitted NDA 21-134 as a reformulation of their sublingual tablets from the currently marketed molded tablets to compressed tablets. Dr. Lipicky believes that because the NDA is primarily a formulation change in the sublingual tablet and that the drug has been marketed with the Nitrostat name for almost 30 years, there is no need for a formal review of the proprietary name by the LNC (now OPDRA).

Preparation:                               /S/  
                                           Edward Fromm

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

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

Talked to Annie Beam of OPDRA on March 24, 2000 about whether Nitrostat, a drug that has been marketed for over 30 years needed a tradename review through OPDRA. I mentioned that the drug was being submitted as an NDA, but primarily as a formulation change.

She said OPDRA prefers the company keep its market name: possible and said that it was not necessary to submit Nitrostat for Tradename Review.
Methods Validation

Dr. Piechocki in his review dated February 9, 2000, states that "it is not deemed necessary to perform a methods validation on this readily soluble product."

Biopharm has reviewed the firm's dissolution method and data and found it to be acceptable (P. Marron 2-7-2000).
Environmental Assessment (EA)

Dr. Piechocki in his February 9, 2000 review states that the firm should be granted exclusion. He noted that “this product is already produced by this firm so that they will only be doing what they have done in the past, at about the same quantities.”