CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21134

CHEMISTRY REVIEW(S)

FEB 9 2000

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

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	02-06-99	03-06-99	15-06-99
AMENDMENT	12-08-99	13-08-99	17-08-99

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 Liason, 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

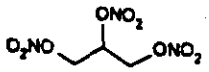
Proprietary:	Nitrostat®
Established:	Propanetriol trinitrate
Code Name/#:	CI-782, PD 79964, DNG
Chem.Type/Ther.Class:	5 S

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 __ OTC
SPECIAL PRODUCTS: ___ Yes _X_ No
(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:



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

MOLECULAR FORMULA: $C_3H_5N_3O_9$

MOLECULAR WEIGHT: 227.09

CAS Number: 55-63-0

SUPPORTING DOCUMENTS:

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

* 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 25^0-25^0C (68^0-77^0F) [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.

/S/

2-9-2000

Joseph T. Piechocki, Review Chemist

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

/S/

2-9-2000

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 now 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 Jeannie 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 marketed tradename possible and said that is 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 firms dissolution method and data and found it to be acceptable (P. Marroum 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."