# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:* **20-574**

## CHEMISTRY REVIEW(S)

OCT 30 1998

**DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS**
**Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 20-574 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 10/26/98

| SUBMISSION/TYPE | DOCUMENT DATE | CDER DATE |
|---|---|---|
| ORIGINAL | 11/25/97 | 11/25/97 |
| Amendment (NC) | 1/30/98 | 2/2/98 |
| Amendment (NC) | 8/7/98 | 8/10/98 |
| Amendment (NC) | 8/17/98 | 8/18/98 |
| Amendment (NC) | 10/23/98 | 10/26/98 |

**NAME & ADDRESS OF APPLICANT:**

Schering-Plough HealthCare Products (SPHCP)
110 Allen Road
Liberty Corner, New Jersey 07938
Ph# (908) 604-1741

**CONTACT:**

Ronald J. Garutti, M.D.
Vice President, Clinical Research/Regulatory Affairs

**DRUG PRODUCT NAME:**

Proprietary: Gyne-Lotrimin 3 Vaginal Cream
Established: Clotrimazole Vaginal Cream, USP
Code #: SCH 15335L; Bay b5097; Bay 5097

**PHARMACOLOGICAL CATEGORY/INDICATION:**

Treatment of vulvovaginal candidiasis.

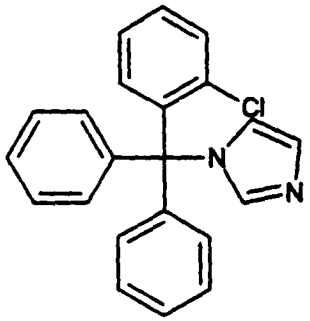
**DOSAGE FORM:** Vaginal Cream

**STRENGTHS:** 2% cream, 100 mg per applicator
**ROUTE OF ADMINISTRATION:** Intravaginal

**Rx/OTC:** OTC

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

CAS-23593-75-1; $C_{22}H_{17}N_2Cl$; MW=344.85
1-(*o*-Chloro-α,α-diphenylbenzyl)imidazole




**SUPPORTING DOCUMENTS:**

[redacted] NDA 17-450; [redacted] NDA 18-520; NDA 18-592; NDA 18-888; NDA 20-288; NDA 20-670

[redacted]

RELATED DOCUMENTS: n/a

**CONSULTS:**

Trademark review (complete 5/14/98, satisfactory).
Site inspection (complete 4/21/98, satisfactory).
Environmental Assessment (categorical exclusion request acceptable).
Microbiology consult (complete 8/21/98, satisfactory).

**REMARKS/COMMENTS:**

This NDA is a resubmitted by Schering-Plough HealthCare Products application, that was originally submitted on April 27, 1995 and withdrawn on January 29, 1996. The sponsor states that the resubmission is in essentially the same format as the original NDA. The CMC review of the original submission was done by Dr. David Katague and is attached to the current review. Items that were reviewed and found acceptable in the original review, are not repeated in the current review. There are two CMC post-approval commitments that were agreed to by the applicant and the FDA regarding the specifications for both drug substance and drug product, which will be submitted through prior-approval supplements to this NDA. These commitments are listed on page 14 of this review and will be included in the NDA action letter.

**CONCLUSIONS & RECOMMENDATIONS:**

The NDA submission and amendments provide adequate information on the chemistry, manufacturing and controls for the production of Gyne-Lotrimin 7 Vaginal Cream. The related GMP and product specific inspections of the manufacturing facilities have been completed and found satisfactory. From the chemistry, manufacturing and controls viewpoint, the NDA is recommended for approval.

/S/

Dorota Matecka, Ph.D.
Review Chemist, HFD-590

/S/ 10/30/98

Norman R. Schmuff, Ph.D.
Team Leader, HFD-590

cc: Org. NDA 20-574
HFD-590/Division File
HFD-590/Team Leader/NSchmuff
HFD-830/DivDir/CChen
HFD-590/Chem/DMatecka
HFD-590/MO/JWinfield
HFD-590/Pharm/OMcMaster
HFD-590/Micro/LGo sey
HFD-590/CSO/CChi
District Office

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**DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS**
Review of Chemistry, Manufacturing, and Controls

**NDA #:** 20-574 **CHEM.REVIEW #:** 01 **REVIEW DATE:** 11-JAN-96

| SUBMISSION/TYPE | DOCUMENT DATE | CDER DATE | ASSIGNED DATE |
|---|---|---|---|
| ORIGINAL | 27-APR-95 | 27-APR-95 | 05-MAY-95 |

**NAME & ADDRESS OF APPLICANT:** Schering-Plough Health Care
110 Allen Road
Liberty Corner, New Jersey

CONTACT PERSON: John M. Clayton, Ph. D.
(908)- 604-1986

**DRUG PRODUCT NAME**

Proprietary: Gyne-Lotrimin 3™
3-Day Vaginal Cream

Nonproprietary: 200mg
Clotrimazole Vaginal Cream

Code Names/#'s: SCH 15335L

Chemical Type/
Therapeutic
Class: 5 S

**ANDA Suitability Petition/DESI/Patent Status:**
N/A

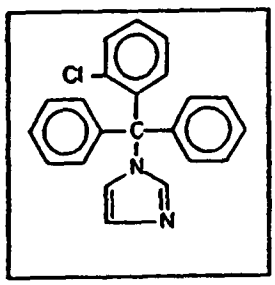
**PHARMACOLOGICAL CATEGORY/INDICATION:** Clotrimazole is a synthetic organic antifungal agent of the imidazole class of drugs, used for the topical treatment of vulvovaginal candidiasis.

| | |
|---|---|
| **DOSAGE FORM:** | Vaginal Cream |
| **STRENGTHS:** | 200 mg |
| **ROUTE OF ADMINISTRATION:** | Intravaginally |
| **DISPENSED:** | _____ Rx __X__ OTC |

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:**

1-(o-chloro-alpha, alpha-diphenylbenzyl)imidazole

M.W= 344.84 $C_{22}H_{17}ClN_2$



**SUPPORTING DOCUMENTS:**

[redacted]

NDA's 17-613; 17-619; 17-717; 18-052; 18-182; 18-183; 18-827; 19-069; [redacted] and 20-525

NDA 18-052, 1% intravaginal clotrimazole cream administered once-a-day for 7 consecutive days for treatment of vulvovaginal candidiasis, was approved on November 8, 1978.

On November 30, 1990, the 1% clotrimazole intravaginal cream administered once-a-day for 7 consecutive days was approved for OTC purchase by non-pregnant women with self-recognized vaginal candidiasis.

[redacted]

**RELATED DOCUMENTS (if applicable):**

NDA 20-525(6), Gyne-Lotrimin 3™ 3-day Vaginal Inserts Plus, Schering-Plough Health Care Products: Document Date: 30-SEP-94.

**CONSULTS:**
None

**REMARKS/COMMENTS:**

The sponsor claims that the administration of the 7-day 1% and 3-day 2% clotrimazole cream have been effective and without significant side effects. In addition, the greater convenience of a 3-day compared to a 7-day regimen may result in greater patient compliance.The sponsor also claims that the 3-day therapy will not compromise either clinical or mycocidal efficacy.

**CONCLUSIONS & RECOMMENDATIONS:**

The application is not approvable for manufacturing and controls under section 505 of the Act. Specific items which are not approvable are identified under the following headings: Drug Product composition, Specifications and Methods, Drug Product Manufacture-in Process Control and testing, Drug product-sampling plan and specifications. An

[redacted]

/S/ 01/11/96

D. B. Katague, Review Chemist

cc: Orig. NDA 20-574
HFD-520/Division File
HFD-520/Katague
HFD-520/MO/Winfield
HFD-520/Pharm/Adeyemo
HFD-520/Micro/Utrup
HFD-520/CSO/Chi
HFD-520/SUPERVISOR/SRoy /S/ 1/11/96
R/D Init by: SUPERVISOR

[redacted]