CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-574**

PHARMACOLOGY REVIEW(S)

JUN 29 1995

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

NDA: 20-574 (000)

DRUG: Gyne-Lotrimin 3 (2% clotrimazole)

CATEGORY: Antifungal cream

SPONSOR: Schering-Plough HealthCare Products
110 Allen Road
Liberty Corner, NJ 07938

NUMBER OF VOLUMES: 68

DATE OF SUBMISSION: April 27, 1995

DATE CDER RECEIVED: April 27, 1995

DATE ASSIGNED: May 2, 1995

DATE REVIEW STARTED: May 12, 1995

DATE FIRST DRAFT COMPLETED: May 22, 1995

DATE REVIEW ACCEPTED BY SUPERVISOR: June 14, 1995

INTRODUCTION/OVERVIEW

Clotrimazole 1% cream was approved in 1978 for treatment of vaginal candidiasis, and was switched to over-the-counter status in 1990. The product (Gyne-Lotrimin Vaginal Cream) is used in a seven day treatment regimen. This NDA seeks approval to market clotrimazole 2% cream for use in a three day treatment regimen.

The total dose of clotrimazole in the seven day 1% regimen is approximately 350 mg, while the total dose in the three day 2% regimen will be 300 mg. Clotrimazole is also administered intravaginally in tablets in single doses as high as 500 mg, in a three day regimen totaling 600 mg, and in a seven day regimen totaling 700 mg.

The sponsor has conducted clinical trials with both the 1% and 2% creams, and has concluded that both regimens were safe and effective.

No new toxicology information was submitted in this NDA, however

reports of 18 animal studies, that were previously submitted between 1975 and 1994, were included in this NDA. Only four of these studies investigated the effects of intravaginal administration of cream formulations of clotrimazole, and these four studies have been evaluated in this review (next section).

PRECLINICAL STUDIES

1. Local and Systemic Tolerance of 2% Vaginal Cream in Dogs

Four groups of beagle bitches (4/group) that had previously littered, received intravaginal treatments with either placebo or clotrimazole, in either a cream or tablet formulation. The treatments were administered once daily for 19 days. The four treatments were as follows:
1) placebo vaginal cream
2) placebo vaginal tablets
3) clotrimazole 200 mg tablets
4) clotrimazole 2% cream 5 grams
Evaluations for treatment-related effects were based upon physical observations including the appearance of the vaginal mucous membrane, body weights, clinical chemistries (SGOT, SGPT, alkaline phosphatase, creatinine, urea), gross pathology, organ weights (11 organs), and complete microscopic histopathology including vagina. Plasma drug concentrations were also measured.

Some slight vaginal changes (erythema and discharge) occurred in all groups including controls, but no treatment-related effects were seen in this study. Plasma concentrations were 5-10 ng/ml four hours after dosing on the first day of the study, and were 20-42 ng/ml four hours after dosing on the 14th day of the study.

2. Two Week Tolerance Study of 4% Vaginal Cream in Dogs

This was a GLP study conducted by Schering in 1981 in New Jersey. Three groups of anestrus female beagles (5/group) were maintained under appropriate environmental conditions. Clotrimazole 4% vaginal cream (5 grams) was administered intravaginally to one group. Another group received a placebo vaginal cream. A third group was used to control for potential mechanical trauma; this group went through the dosing procedure, but with an empty syringe. Treatments were given once daily for 14 days. Evaluations for treatment-related effects were based upon physical observations including the appearance of the vaginal mucous membrane, body weights, food consumption, gross pathology, and microscopic examination of vaginal tissue sections.

Some vaginal changes (erythema, edema, inflammation) were seen microscopically in all groups including controls. In two of the

five dogs treated with clotrimazole, mild basal cell hyperplasia occurred and was thought to be secondary to the inflammation that was present.

3. Three Week Toxicity Study of 10% Vaginal Cream in Dogs

This was a non-GLP study conducted by [redacted] from December 1982 to January 1983. Eight female beagle dogs (approximately 4-8 years of age) that had previously littered, were divided into two groups of four. Clotrimazole 10% vaginal cream (approximately 4.6 grams) was administered intravaginally once daily for three weeks to one group, while the other group received a placebo cream. Based on the body weights, these treatments corresponded to doses of approximately 35-50 mg/kg. Evaluations of this treatment were based on physical observations including the vaginal mucous membrane, body weights, food consumption, hematology, coagulation, clinical chemistry, urinalysis, gross pathology, organ weights, and microscopic histopathology. Plasma drug concentrations were determined.

Erythema of the vaginal mucosa was observed in both groups, but the incidence was higher in the treated animals. No treatment-related effects occurred in the parameters examined. Plasma concentrations were <10-31 ng/ml four hours after dosing on the first day of the study, and were 24-59 ng/ml four hours after dosing on the 17th day of the study.

4. One Month Toxicity Study of 1% and 10% Vaginal Creams in Dogs

This was a GLP study conducted in 1993 by [redacted] for Schering. Twenty young (5-6 months old) anestrus female beagles, housed under appropriate environmental conditions were randomized into five groups each containing four animals. Two of the groups were treated with creams containing clotrimazole, while the other three groups served as controls. The treatments were administered intravaginally in a volume of 5 ml, once daily for one month as follows:

1) clotrimazole cream 10%
2) clotrimazole cream 1%
3) placebo vaginal cream
4) sham-dosed control (manipulated with an empty syringe)
5) naive control (no treatment whatsoever)

The effects of the treatments were evaluated based on physical observations, eye examinations, body weights, food consumption, hematology, serum chemistry, urinalysis, gross pathology, organ weights, and microscopic examination of kidney, urinary bladder, and reproductive tract.

No effects were seen in this study that could be attributed to clotrimazole treatment.

CONCLUSIONS/RECOMMENDATIONS TO SPONSOR

The four studies evaluated in this review, show that in beagle dogs, the intravaginal administration of creams containing clotrimazole in concentrations of 1%, 2%, 4%, and 10% produced no systemic toxicity, and only very mild signs of vaginal irritation.

Based on the toxicology studies and on the long-term human experience with this product, approval of this NDA is recommended.

/S/

Kenneth Seethaler, Ph.D., D.A.B.T.
Pharmacologist, HFD-520

cc: Original NDA 20-574 (000)
HFD-340
HFD-520
HFD-520/Pharm/K.Seethaler
HFD-520/MO/J.Winfield
HFD-520/Micro/A.Sheldon /S/ 6/28/95
HFD-520/Chem/D.Katague
HFD-520/CSO/C.Chi

Concurrence Only:
HFD-520/DD/L.Gavrilovich
HFD-520/SPharm/R.Osterberg /S/ 6/14/95

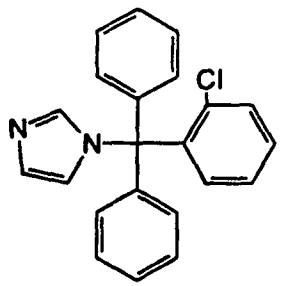
Submitted: November 25, 1997
Assigned: November 26, 1997
Completed: October 5, 1998
HFD-590

Sponsor: Schering Plough Corporation
110 Allen Road
PO Box 276
Liberty Corner, New Jersey 07938-0276

Drug: Gyne Lotrimin 3-day Vaginal cream
Generic Name: 2 % Clotrimazole
Code Number: SCH 15335L
Chemical Names: Clotrimazole; 1-(o-chloro-alpha, alphadiphenylbenzyl) imidazole
Molecular formula: $C_{22}H_{17}ClN_2$
Molecular weight: 344.84
CAS Registry Number: CAS-23593-75-1
Physical and chemical characteristics: Smooth white to off-white cream free of foreign matter and agglomerates

Formulation: Clotrimazole 2 % cream contains: purified water, USP [redacted] octyldodecanol, NF [redacted] cetearyl alcohol 70/30 [redacted] cetyl esters wax, NF [redacted] clotrimazole, USP [redacted] sorbitan monostearate, NF [redacted] polysorbate 60, NF [redacted] benzyl alcohol, NF [redacted]

Structure:



Introduction:

Clotrimazole is a synthetic organic antifungal of the imidazole class, which exhibits activity against a number of pathogenic dermatophytes, yeasts and *Malassezia furfur*. Clotrimazole exhibits fungicidal and fungistatic activity against *Candida* species. There are currently a number of prescription and over the counter clotrimazole products marketed for the treatment of vulvovaginal yeast infections, including a 1 % cream to be administered in

50 mg doses once daily for 7 days and a vaginal insert (100 mg clotrimazole/insert) which is used once daily for 7 days. The current application is for a 2 % cream which will be inserted once daily (100 mg clotrimazole) for three days for the treatment of vulvovaginal candidiasis.

The toxicology of clotrimazole has been extensively studied and no new data was submitted. The studies using cream formulations were reviewed by [redacted] and are attached.

Based on the extensive clinical experience with this product and the results of the toxicology studies, approval of this NDA is recommended.

/S/

Owen G McMaster, Ph.D.
Pharmacology Toxicology Reviewer.

Concurrences:
HFD-590/RAlbrecht 11/3/98
HFD-590/KHastings 10/26/98

Disk:
HFD-590/KHastings

cc:
HFD-590 Original IND
HFD-590 Division File
HFD-340
HFD-590/Biopharm/FAjayi
HFD-590/Chem/DMatecka
HFD-590/CSO/CChi
HFD-590/Micro/LGosey
HFD-590/MO/JWinfield
HFD-590/Pharm/OMcMaster