CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-574**

MICROBIOLOGY REVIEW(S)

JUL 16 1998

REVIEW TO HFD-590
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST REVIEW OF AN NDA
July 6, 1998

A. NDA 20-574

PRODUCT NAME: Clotrimazole 3-Day Vaginal Cream

APPLICANT: Schering Plough
Liberty Corner, New Jersey 07938

DOSAGE FORM: 21 g Tube of Vaginal Cream and 3 Disposable Applicators

PHARMACOLOGICAL CATEGORY: Topical Antifungal Vaginal Cream

B. APPLICATION DATE: November 25, 1997 (resubmission of NDA)
ASSIGNED FOR REVIEW: May 21, 1998

C. REMARKS: The supplier of drug substance, Clotrimazole USP, is identical to the supplier in the currently marketed 1% clotrimazole (Gyne-Lotrim® Vaginal Cream, NDA 18-052). Manufacturing, processing, packaging, and control operations for the drug product are conducted at Schering-Plough Products, Inc., Carretera Estatal 686 Kilometro 0.5, Manati, Puerto Rico. The facilities and equipment are the same as those currently used to manufacture and package the approved clotrimazole 1% cream (Gyne-Lotrimin® 1% Cream, NDA 18-052). Product quality information such as microbial limits and preservative effectiveness are the subject of this microbiology review.

D. CONCLUSIONS: The NDA 20-574 which provides for Clotrimazole 3-Day Vaginal Cream is not recommended for approval from the standpoint of product quality microbiology.

/S/ 7/6/98

Patricia F. Hughes, Ph. D.
Review Microbiologist
7/6/98

cc.: Original NDA 20-574
HFD-160 /Consult File
HFD-160/PFHughes
HFD-590/CChi/DMatecka
HFD-590/Division File
Drafted by PFHughes. 7/06/98
R/D Initialed by PHCooney

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AUG 27 1998

REVIEW TO HFD-590
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST REVIEW OF AN AMENDEMEMT
August 21, 1998

A. NDA 20-574

PRODUCT NAME: Clotrimazole 3-Day Vaginal Cream

APPLICANT: Schering Plough Health Care Products
Liberty Corner, New Jersey 07938

DOSAGE FORM: 21 g Tube of Vaginal Cream and 3 Disposable Applicators

PHARMACOLOGICAL CATEGORY: Topical Antifungal Vaginal Cream

B. SUBMISSION DATE: August 7, 1998
ASSIGNED FOR REVIEW: August 7, 1998

C. REMARKS: This amendment to the NDA 20-574 contains responses to deficiencies found in the original NDA submission.

D. CONCLUSIONS: The NDA 20-574 which provides for Clotrimazole 3-Day Vaginal Cream is recommended for approval from the standpoint of product quality microbiology. The applicant commits to conduct Antimicrobial Effectiveness (APE) Testing on the first marketed production batch and submit results to the FDA post approval. Updated APE data on stability batch [redacted] will also be submitted post approval. In addition, the applicant commits to include selective media for yeast and mold recovery as part of the Microbial Limits Test for the production batches of this product. Please see section E for Review Notes.

/S/ 8/24/98

Patricia F. Hughes, Ph. D.
Review Microbiologist

8/27/98

cc.: Original NDA 20-574
HFD-160 /Consult File
HFD-160/PFHughes
HFD-590/CChi/DMatecka
HFD-590/Division File
Drafted by PFHughes. 08/21/98
R/D Initialed by PHCooney

NOV 12 1998

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS
(HFD-590)

NDA #20-574

REVIEWER: Linda J. Utrup, Ph.D.

CORRESPONDENCE DATE: 24 NOV 1997
CDER RECEIPT DATE: 25 NOV 1997
REVIEW ASSIGN DATE: 19 JUNE 1998
DATA RECEIPT DATE: 9 JULY 1998
REVIEW COMPLETE DATE: 27 AUG 1998

SPONSOR: Schering-Plough Corporation
110 Allen Road
Liberty Corner, New Jersey 07938-0276

SUBMISSIONS REVIEWED: 000

DRUG CATEGORY: Vaginal antifungal

INDICATION: Over-the-counter treatment of vaginal candidiasis for 3 days.

DOSAGE FORMS: Topical 2% cream (100 mg) (for 3 days)

PRODUCT NAMES:

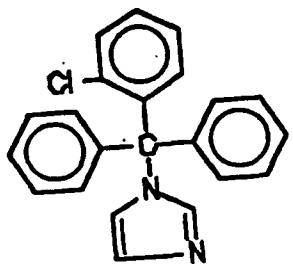
a. PROPRIETARY: GyneLotrimin 3
3-Day Vaginal Cream

b. NONPROPRIETARY: clotrimazole

c. Chemical Name: 1-[(2-chlorophenyl)diphenylmethyl]-1H-imidazole

Molecular Weight 344.84

Chemical Structure:



SUPPORTING DOCUMENTS:

[redacted]
NDA 18-052
NDA 17-717
NDA 17-717, S006
NDA 20-289
NDA 20-526
NDA 19-069
NDA 18-230
NDA 18-182

BACKGROUND:

Both Gyne-Lotrimin and Mycelex (clotrimazole) products were introduced in the late 1970's as prescription products that have since been granted over-the-counter (OTC) status. Gyne-Lotrimin 1% Vaginal Cream is currently marketed OTC with the regimen of 1 applicatorful of cream (50 mg) inserted vaginally once daily for 7 days (the total treatment regimen is 350 mg clotrimazole).

There are currently two marketed Gyne-Lotrimin vaginal insert products. One contains 100 mg clotrimazole inserts with the approved treatment regimen for vulvovaginal candidiasis of 1 Gyne-Lotrimin insert applied intravaginally once a day for 7 days (total dosage per treatment is 700 mg).

An alternative treatment regimen in use when the Gyne-Lotrimin 100 mg insert product was available by prescription only was 200 mg clotrimazole administered intravaginally as two 100 mg clotrimazole inserts once daily for 3 days (total dosage for 3-day treatment was 600 mg).

The second product, Gyne-Lotrimin 3 (a 3-day vaginal insert) designed to mimic the prescription use of 2 x 100 mg vaginal tablets, was approved for OTC treatment in 1996. Gyne-Lotrimin 3 vaginal insert is comprised of a 200 mg vaginal tablet administered for 3 consecutive days. Total dosage for this product for a 3-day treatment regimen is 600 mg.

The Gyne-Lotrimin vaginal insert products are also each marketed in a combination pack with a 1% clotrimazole cream for use to relieve external vulvar itching. The 7-day combination product was approved in 1993 and the 3-day combination products were approved in 1996.

In addition, a 500 mg clotrimazole vaginal insert for single application was previously marketed under the Gyne-Lotrimin brand name held by [redacted]

The Mycelex brand of 1% clotrimazole vaginal cream is also available OTC (NDA 18-230). The approved treatment is 1 applicatorful (5 g of 1% cream or 50 mg clotrimazole inserted intravaginally daily for 7 days).

The Mycelex brand vaginal insert is currently marketed OTC under the name Mycelex-7 vaginal insert and contains 100 mg clotrimazole/insert. The approved treatment regimen is 1 insert/day for 7 days (total dosage per treatment 7 days is 700 mg). This product is marketed under NDA 18-182.

As with the Gyne-Lotrimin brand, an alternate treatment regimen while the product was available by prescription was 200 mg clotrimazole administered intravaginally as two 100 mg Mycelex-G inserts daily for 3 days (total dosage per 3 day treatment is 600 mg). [redacted] also continues to market (Rx) a 500 mg clotrimazole vaginal insert for one-time administration.

Schering-Plough submitted NDA 20-574 for GyneLotrimin 3 Vaginal Cream 2%. This was a 3 day therapy for vaginal yeast infections (candidiasis). In one study, the results indicated that the use of the 1% cream for 7 days was equivalent to the 2% cream used for 3 days. The other study indicated that the 1% cream used for 7 days was equivalent to the 1% cream used for 3 days. Because two studies were required by the FDA, the data submitted did not support approval for either the 1 day or the 3 day applications based on equivalence to the 7 day application. The applicant withdrew the application. Subsequently Schering Plough and Taro entered into a joint venture for both companies to provide the data needed to support the approval of a 3-day clotrimazole 2% vaginal cream.

Taro markets clotrimazole vaginal cream in 1% and 2% formulations in Canada and in a 1% formulation in the US. The Canadian products were marketed as prescription products until 1995, at which time they were granted over-the-counter status by the Health Protection Branch. The US 1% product has been marketed as an over-the counter product since 1995. A 10% clotrimazole vaginal cream [redacted] is also marketed by BayPharm, UK.

The FDA agreed to pool the two Schering clinical studies (93-34 and 93-40) as a single study and use Taro's study (95-50) as the other study. The FDA recommended that the two companies perform a "bridging" study to demonstrate therapeutic equivalence between the two different product formulations. The FDA will not accept *in vitro* data alone as the "bridging" study. The sponsors have decided to market the formulation by Schering.

Following intravaginal application, only about 3-10% of the applied dose of clotrimazole is systemically absorbed. The major site of metabolism is the liver which rapidly biotransforms the active drug to inactive metabolites. Blood levels of clotrimazole following intravaginal application are 3-10% of the applied dose (3 -10 mg of a 100 mg dose). See the BioPharm review for further information. These systemic subtherapeutic levels should not effect the average person, but theoretically could lead to the development of resistance in immunocompromised patients.

Clotrimazole exhibits a broad-spectrum of antifungal activity against various species of pathogenic dermatophytes, yeasts and *Malassezia furfur*. Its primary action is against dividing and growing organisms. The sponsor does not give any MIC information but does state in the submission that clotrimazole exhibits fungistatic and fungicidal activity against most *Candida* species, including pathogenic *C. albicans* and other pathogenic fungi. However, it should be noted that the sponsor does not wish to include either fungistatic of fungicidal claims in the package insert. Additionally, there were no kill curves, MICs or MBCs included in the submission. No susceptibility testing was requested by the FDA or performed by the sponsor.

Clotrimazole is active against most susceptible strains of *Candida sp.*, including *C. albicans, C. glabrata, C. tropicalis, C. parasilosis*. Recurring candidiasis has been associated with non *C. albicans* species. However, Schmidt found no clotrimazole MICs > 4 mcg/mL in 142 clinical isolates tested, C. *albicans* (96 strains), *C. glabrata* (12 strains), *C. krusei* (12 strains) and *C. tropicalis* (12 strains). White et.al. stated that there was decreased susceptibility to clotrimazole therapy observed in two HIV infected patients. Reports suggest that greater than 50% of the patients with *C. glabrata* infection fail clotrimazole therapy. It has been hypothesized that since there is a two dilution higher MIC, this means the isolates are resistant to clotrimazole and this is the reason for failure. There are, however, many patients infected with *C. albicans* who also fail therapy. Lynch, *et. al.* and Fong, *et. al.*, concluded that episodes of recurrent vulvovaginal candidiasis caused by *C. albicans* are rarely attributable to azole antifungal resistance. If this conclusion is correct, another mechanism, other than resistance, may be responsible for mycological failures. It is possible that this same mechanism is the reason some of the patients with non-albicans species fail therapy. Since there are no standardized susceptibility testing methods for clotrimazole against vaginal candidiasis, no NCCLS quality control ranges or interpretive criteria established for clotrimazole, and no MIC values reported for the isolates obtained in these clinical studies; no definitive conclusions can be made from these trials regarding mycological failure as it relates to resistance.

Protocol 93-34 was conducted in two parts. In the first part, the safety and efficacy of the 3-day 1%, 2% and 4% therapies and the 7-day 1% therapy were compared to determine the lowest concentrations of clotrimazole used for 3 days that was at least as effective as the 7-day therapy. In the second part, additional data were obtained on the comparative safety and efficacy of the most effective 3-day therapies identified in the first part of the study, and the 7-day therapy. The data from parts 1 and 2 were pooled by the sponsor which they proposed to use as the first of two adequate and well-controlled pivotal trials.

Studies 93-34 and 93-40 included non-pregnant patients who had not had an episode of vulvovaginal candidiasis in the 60 days before study entry. Before the start of therapy patients were cultured for *Candida* and 10% KOH wet mounts were prepared. Patients were scheduled for follow-up at 14-17 and 28-31 days after the start of therapy. In order to accommodate scheduling of visits, the 14-17 day visit was accepted if it occurred within 10-20 days and the 28-31 day visit was accepted if it occurred at or beyond day 21. At each follow-up visit, KOH wet mounts for *Candida* pseudohyphae were repeated, and vaginal smears were obtained for culture for *Candida*. According to the sponsor, a mycological cure is a patient

who had a negative KOH wet mount for pseudohyphae and a negative culture for *Candida* at the day 10-20 visit and at her final visit at least 21 days after the start of therapy. A relapse was a patient who had a negative KOH wet mount and negative culture for *Candida* at the day 10-20 visit, and had a positive KOH wet mount and/or culture for *Candida* at her final visit. A clinical cure was a patient who had improve symptoms at her final visit (at least 21 days after the start of therapy). "Improved symptoms" was defined as a reduction in the mean score of symptoms of vulvovaginal candidiasis from the pre-therapy visit. A therapeutic cure was a patient who was both clinically and mycologically cured. Patients who were either clinical or mycological failures at either post therapy follow-up visit were classified as therapeutic failures.

There was no microbiology section included in the NDA submission. The data presentation of the various studies (Schering Plough, Taro and bridging) was not consistent and it was difficult to determine the evaluable patient population and mycological outcomes. The sponsor did not summarize the culture data.

According to the sponsor, there were a number of patients excluded from the efficacy analyses of Studies 93-34 and 93-40. The most frequent reason for excluding patients was a negative culture for *Candida* at study entry. The culturing media used was BiGGY agar which does not support the growth of *Candida* as well as the Sabouraud's agar used in the Taro study (95-50). The lack of culturing media sensitivity may explain, at least in part, the relatively large number of patients excluded from Studies 93-34 and 93-40 due to a negative pre-treatment culture. There were no statistically significant differences among the study arms regarding the excluded patients. See the Statistical Officer's review for actual numbers.

Of those patients with a positive vaginal culture at study entry (Studies 93-34 and 93-40), C. *albicans* was isolated 97% (597/616) of the time and the non-albicans species were isolated 3% (19/616) of the time. According to the sponsor (Study 93-34), *C. albicans* eradication rates were 47% in the 7-day 1% group, 39% in the 3-day 1% group, 47% in the 3-day 2% group, and 54% in the 3-day 4% group. Also according to the sponsor (Study 93-40), *C. albicans* eradication rates were 52% in the 7-day 1% group, 48% in the 3-day 1% group, 45% in the 3-day 2% group. The Microbiology review was completed prior to the Medical Officer's review. Therefore, the Medical Officer's evaluable patient population and resulting analysis will not be included in the Microbiology review.

The Microbiology Reviewer's analysis of the data from Study 93-34 is included in Table 1.

Table 1. Mycology results from Study 93-34

Treatment	Eradicated	Not Eradicated		Total
	Pretreatmcnt *C. albicans* (# reinfected)	Pretreatment *C. albicans*	Pretreatment Non-albicans	
1% 7 day	53 (5)	44	2	99
1% 3 day	46 (5)	56	1	103
2% 3 day	55 (6)	41	3	99
4% 3 day	17 (1)	11	1	29
Total	171 (17)	152	7	330

Table 1 shows that of the 99 patients on the 1% 7 day treatment with pretreatment *Candida* isolates, the organisms were eradicated in 54% (53/99) and not eradicated in 46% (46/99) of the patients. Two patients on the 1% 7day therapy had pre-treatment non-albicans isolates which were not eradicated. Of the 99 patients on the 2% 3 day treatment with pre-treatment isolates, *Candida* was eradicated in 56% (55/99) and not eradicated in 44% (44/99) of the patients post-treatment. The 3 patients on the 2% 3day therapy with pre-treatment non-albicans isolates were not eradicated of the organisms post-treatment.

The Microbiology Reviewer's analysis of eradication was defined as a patient who had a negative culture for *Candida* for both visits 2 and 3. No eradication was defined as a patient who had a positive culture for *Candida* at visit 2 and/or visit 3. Reinfection was defined as an eradication of the original organism and a reinfection with a different Candida species. In Tables 1, 2, 3 and 4, reinfections are included in the eradicated rates and are listed in the parentheses. The sponsor's analysis of mycological cure (eradication) was the same except that both the KOH and culture had to be negative at visits 2 and 3. A positive KOH and/or culture result would be a mycological failure at visit 2 or a mycological relapse at visit. 3. Therefore a patient with a positive KOH and negative culture at visit 2 would be considered by the reviewer to have the *Candida* eradicated; the sponsor would consider the organisms not eradicated. Consequently, the reviewer's eradication rates are higher than those of the sponsor.

A total of seven patients had pre-treatment non-albicans (*C. glabrata*) isolates; these isolates were not eradicated following therapy. There were 17 patients with pre-treatment *C. albicans* isolates who had a different species of *Candida* post-treatment. These patients were considered to be eradicated of the original isolate and reinfected with a different species of *Candida*. According to the agreement with the sponsor, the results of studies 93-34 and 93-40 are combined and represent one clinical study (see Table 3).

There were no clotrimazole MICs included in the submission. In the literature, there are some reports of higher MICs with non-albicans species; however, without standardized susceptibility testing methods and approved interpretive criteria for clotrimazole against vaginal candidiasis, it is difficult to make any definitive conclusions regarding resistance.

The Microbiology Reviewer's analysis of the data from Study 93-40 is included in Table 2.

Table 2. Mycology results from Study 93-40

Treatment	Eradicated		Not Eradicated		Total
	Pretreatment *C. albicans* (# reinfected)	Pretreatment Non-albicans (# reinfected)	Pretreatment *C. albicans*	Pretreatment Non-albicans	
1% 7 day	54 (1)	3	42	2	101
1% 3 day	54 (0)	1	50		105
2% 3 day	51 (4)	4 (1)	51	3	109
Total	159 (5)	8 (1)	143	5	315

Table 2 shows that of the 101 patients on the 1% 7 day treatment with pre-treatment isolates, the organisms were eradicated in 56% (57/101) and not eradicated in 44% (44/101) of the patients. Of the 5 patients on the 1% 7day therapy with pre-treatment non-albicans isolates; the organisms were eradicated in 3 and not eradicated in 2 of the patients. Of the 109 patients on the 2% 3 day treatment with pre-treatment isolates, *Candida* was eradicated in 50% (55/109) and not eradicated in the other 50% (54/109) of the patients. Of the 7 patients on the 2% 3day therapy with pre-treatment non-albicans isolates; the organisms were eradicated in 4 and not eradicated in 3 of the patients.

A total of 13 patients had pre-treatment non-albicans isolates; the *Candida* was eradicated in 8 and not eradicated in 5 patients following therapy. There were 5 patients with pre-treatment *C. albicans* and one patient with a non-albicans isolate who had a different species of *Candida* post-treatment. These patients were considered to be eradicated of the original isolate and reinfected with a different species of *Candida*. According to the agreement with the sponsor, the results of studies 93-34 and 93-40 are combined and represent one clinical study (see Table 3).

As noted previously, there were no clotrimazole MICs included in the submission. There are some reports of higher MICs noted in the literature with non-albicans species; however, without standardized susceptibility testing methods and approved interpretive criteria for clotrimazole in vaginal candidiasis indications, it is difficult to make any definitive conclusions regarding resistance.

The combined results for the 93-34 and 93-40 studies are shown in Table 3.

Table 3. Mycology results from Studies 93-34 and 93-40

Treatment	Eradicated		Not Eradicated		Total
	Pretreatment *C. albicans* (# reinfected)	Pretreatment Non-albicans (# reinfected)	Pretreatment *C. albicans*	Pretreatment Non-albicans	
1% 7 day	107 (6)	3	86	4	200
1% 3 day	100 (5)	1	106	1	208
2% 3 day	106 (10)	4 (1)	92	6	208
Total	313 (21)	8 (1)	284	11	616

Table 3 shows that of the 200 patients on the 1% 7 day treatment with pre-treatment isolates, the organisms were eradicated in 55% (110/200) and not eradicated in 45% (90/200) of the patients. Of the 7 patients on the 1% 7day therapy with pre-treatment non-albicans isolates; the organisms were eradicated in 3 and not eradicated in 4 of the patients. Of the 208 patients on the 2% 3 day treatment with pre-treatment isolates, *Candida* was eradicated in 53% (110/208) and not eradicated in 47% (98/201) of the patients. Of the 10 patients on the 2% 3day therapy with pre-treatment non-albicans isolates; the organisms were eradicated in 4 and not eradicated in 6 of the patients.

A total of 19 patients had pre-treatment non-albicans isolates; these organsims were eradicated in 42% (8/19) and not eradicated in 58% (11/19) of the patients. There were 21 patients with pre-treatment *C. albicans* and one patient with a non-albicans isolate who had a different species of *Candida* post-treatment. These patients were considered to be eradicated of the original isolate and reinfected with a different species of *Candida*.

It should be noted that in all cases the number of patients with non-albicans species is much smaller than those with *C. albicans* and therefore the percentages reported here may be less reliable than those of *C. albicans*. There were no clotrimazole MICs included in the submission. Without approved susceptibility testing methods, quality control ranges and interpretive criteria for determination of clotrimazole activity against relevant *Candida sp.*, it is difficult to make any definitive conclusions regarding resistance.

The Microbiology Reviewer's analysis of eradication was defined as a patient who had a negative culture for *Candida* for both visits 2 and 3. No eradication was defined as a patient who had a positive culture for *Candida* at visit 2 and/or visit 3. The sponsor's analysis of mycological cure (eradication) was the same except that both the KOH and culture had to be negative at visits 2 and 3. A positive KOH and/or culture

result would be a mycological failure at visit 2 or a mycological relapse at visit. 3. Reinfection was defined as an eradication of the original organism and a reinfection with a different Candida species.

Study 95-50 (Taro)

The most frequent reason for exclusion of patients from the efficacy analysis in this study was missed visits or visits that fell outside the protocol windows. Cultures for *Candida* were positive for all patients who began treatment.

The results for the Taro Study 95-50 are shown in Table 4.

Table 4. Mycology results from Study 95-50 (Taro Study)

Treatment	**Eradicated**		**Not Eradicated**		**Total**
	Pretreatment *C. albicans* (# reinfected)	Pretreatment Non-albicans (# reinfected)	Pretreatment *C. albicans*	Pretreatment Non-albicans	
S-P 1% 7 day	50		26	1	77
Taro 2% 3 day	49		21	1	71
Taro 2% 1 day	36	1	25	1	63
Total	135 (0)	1 (0)	72	3	211

According to the Microbiology Reviewer, the eradication rate was 69% (49/71) for the 2% 3-day treatment, 65% (50/77) for the 1% 7-day treatment, and 59% (37/63) for the 2% 1-day treatment. The eradication rates for *Candida albicans* were 65% (50/77) in the 7-day 1% group and 69% (49/71) in the 3-day 2% group. In this study a total of 4 patients had pre-treatment non-albicans isolates; the *Candida* was eradicated in one patient and not eradicated in 3 patients. A total eradication rate for the Taro study was 64% (136/211) and the non-eradication rate was 36% (75/211).

In the bridging study 97-01, the Schering and Taro 2% 3 day products were compared. There were 71 patients in each arm that had pretreatment *C. albicans*. There was only one isolate of *C. glabrata* identified. That patient had only an initial visit and no follow-up visits. According to the Medical Officer, the mycological cure rates were 77% (51/66) for the Taro product and 75% (51/68) for the Schering product. The therapeutic effectiveness of the two formulations of 2% clotrimazole vaginal cream used once daily for three consecutive days demonstrate that the products are equally effective treatments of vulvovaginal candidiasis. There were no statistically significant differences between the two formulations in clinical, mycological or therapeutic cure rates.

CONCLUSIONS

In summary, considering all of the data from all of the studies submitted to this NDA, the 1% 7 day therapy produced a 55% (107/193) (Schering Plough) and 66% (50/76) (Taro) mycological eradication rate in patients with pre-treatment *C. albicans*. For the patients with pre-treatment non-albicans isolates, *Candida* was eradicated in 43% (3/7) (Schering Plough) and not eradicated in the one patient in the Taro study.

For the 2% 3 day therapy, 54% (106/198) (Schering Plough) and 59% (36/61) (Taro) of the patients with pre-treatment *C. albicans* were eradicated of the organisms. For the patients with pre-treatment non-albicans isolates, *Candida* was eradicated in 40% (4/10) (Schering Plough) and in one of the two patients in the Taro study.

In all of the studies, the cure rate for the non-albicans isolates was slightly less than for *C. albicans*. However, the number of patients in the non-albicans groups was small and therefore the results may be less reliable than those for *C. albicans*. Since there is a lower cure rate for these species and the MICs are higher for non-albicans isolates, one hypothesis suggests that the lack of cure is due to resistance. However, without standardized susceptibility testing methods, approved interpretive criteria, and MIC values for the relevant clinical isolates, it is difficult to make any definitive conclusions regarding the role of drug resistance in clinical outcome.

The overall conclusion is that the 2% 3 day therapy is comparable to the 1% 7 day therapy and it has approval from the microbiology perspective.

There is no traditional microbiology section to review in this OTC label. No microbiology additions will be made to the label.

REFERENCES

Lynch et.al. J. Med Vet Mycol 1996 Sep;34(5):337-339.
Fong IW et. al. Genitoruin Med. 1993 Feb69 (1):44-46.
Schmidt A. Arzneimeittelforschung 1995 Dec;45(12):1338-1340.
White et. al. Clin Infect Dis 1994 Oct;19(4):687-692.

RECOMMENDATIONS:

This application has approval from the microbiological perspective. There are no microbiology changes to be made to the labeling.

/S/

Linda J. Utrup, Ph.D.

CONCURRENCES ONLY:

HFD-590/Dep Div Dir /S/ Signature 11/12/98 Date
HFD-590/MTL_____ Signature 11/12/98 Date

CC:

HFD-590 NDA #20-574
HFD-590/MO/Winfield
HFD-590/CSO/Chi
HFD-590/MTL/Lard
HFD-590/Micro/Utrup

590 chi

Nov 19, 1998

NOV 19 1998

REVIEW TO HFD-590
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST REVIEW OF AN AMENDEMEMT (#2)
November 19, 1998

A. NDA 20-574

PRODUCT NAME: Clotrimazole 3-Day Vaginal Cream

APPLICANT: Schering Plough Health Care Produc
Liberty Corner, New Jersey 07938

DOSAGE FORM: 21 g Tube of Vaginal Cream and 3 Disposable Applicators

PHARMACOLOGICAL CATEGORY: Topical Antifungal Vaginal Cream

B. SUBMISSION DATE: October 28, 1998
ASSIGNED FOR REVIEW: November 17, 1998

C. REMARKS: This amendment to the NDA 20-574 contains additional APE test data requested as a result of deficiencies found in the original NDA submission.

D. CONCLUSIONS: The amendment dated October 28, 1998 to NDA 20-574 which provides for Clotrimazole 3-Day Vaginal Cream is recommended for approval from the standpoint of product quality microbiology. Please see section E for Review Notes.

/S/ 11/19/98
Patricia F. Hughes, Ph. D.
Review Microbiologist
11/19/98

cc.: Original NDA 20-574
HFD-160 /Consult File
HFD-160/PFHughes
HFD-590/CChi/DMatecka
HFD-590/Division File
Drafted by PFHughes. 11/19/98
R/D Initialed by PHCooney