

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-735

MICROBIOLOGY REVIEW

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

NDA #: 21-735

REVIEWER : Kalavati Suvarna
CORRESPONDENCE DATE : 11-26-03, 09-02-04
CDER RECEIPT DATE : 12-02-03, 09-07-04
REVIEW ASSIGN DATE : 02-02-04, 09-15-04
REVIEW COMPLETE DATE : 09-15-04

SPONSOR: Altana, Inc.
60 Baylis Road
Melville, NY 11747.

SUBMISSION REVIEWED: N-000, N-000 (BM)

DRUG CATEGORY: Anti-fungal

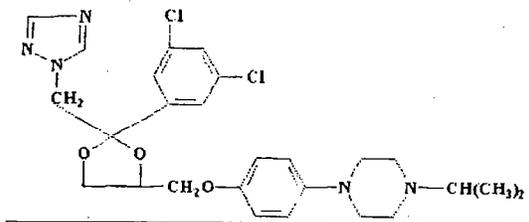
INDICATION: Treatment of vulvovaginal candidiasis

DOSAGE FORM: Vaginal Cream (0.8%)

PRODUCT NAMES:

- a. **PROPRIETARY:** None
- b. **NONPROPRIETARY:** Terconazole
- c. **CHEMICAL:** cis-1-[p-[2-(2,4-Dichlorophenyl)-2-(1H,1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy] phenyl]-4- isopropylpiperazine

STRUCTURAL FORMULA:



Molecular weight: 532.47
Empirical formula: C₂₆H₃₁Cl₂N₅O₃

SUPPORTING DOCUMENTS: DMF# _____

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1. EXECUTIVE SUMMARY:

The subject of this NDA is a new formulation of Terconazole (0.8% external cream) for the treatment of vulvovaginal candidiasis (VVC). Terconazole, is the active ingredient in Terazol[®] 3, an approved product for the treatment of VVC.

The support for the preclinical microbiology aspects of the application is based on the approved label for Terazol[®] 3 vaginal cream. In the clinical study, the VVC infection in a majority of patients was due to *C. albicans*.

There were few patients with infections due to *Candida* species other than *C. albicans*. However, the species were not identified. The percentage of patients with resolution of VVC symptoms and eradication of baseline *C. albicans* in the new terconazole product arm (76%) was higher than the Terazol[®]3 arm (63%). The clinical and mycological outcome in patients with baseline infection due to *Candida* species other than *C. albicans* was similar in the two groups (new terconazole product arm, 33.3%; Terazole[®] 3 arm, 36%). *In vitro* susceptibility testing of isolates collected at baseline and at 18 to 27 days after discontinuation of treatment was not performed. In both treatment arms, 11% patients that showed a successful clinical and mycological outcome at 5 to 7 days after therapy relapsed at 18 to 27 day after discontinuation of therapy.

2. INTRODUCTION AND BACKGROUND:

The subject of this NDA is Terconazole (0.8% vaginal cream) for the treatment of vulvovaginal candidiasis (VVC). The applicant developed a new formulation of terconazole 0.8% vaginal cream and initially filed an ANDA with the Office of Generic Drugs for the product. The applicant received a refuse to file letter since this product was found to be superior to the marketed product and did not meet the criteria for bioequivalence. In this submission, the sponsor has included a multi-center clinical study to evaluate the safety and efficacy of the new 0.8% Terconazole vaginal cream formulation compared to Terazol[®]3. Terazol[®]3 is a marketed antifungal cream containing 0.8% terconazole effective in the treatment of VVC, when applied intravaginally once daily at bedtime for 3 consecutive days.

3. PRECLINICAL MICROBIOLOGY:

The sponsor is relying on the approved label for Terazol[®]3 vaginal cream, to support the preclinical microbiology section of the label. No additional preclinical microbiology studies were included in this submission.

3.1. Mechanism of action:

Terazole may exert its antifungal effect by disruption of the fungal membrane. (See Terazol[®]3 vaginal cream approved label).

3.2. Activity *in vitro*:

In vitro, terconazole is active against *Candida albicans* and other fungi. Against *Lactobacillus* species, the terconazole MICs were ≥ 128 $\mu\text{g/ml}$ (See Terazol[®]3 vaginal cream approved label).

3.3. Activity *in vivo*:

No studies were conducted to evaluate the activity of terconazole against *Candida* species *in vivo*.

3.4. Drug Resistance and Cross-resistance:

No resistance to terconazole has developed during successive passages of *C. albicans* (See Terazol[®]3 vaginal cream approved label).

4. CLINICAL MICROBIOLOGY:

The sponsor conducted a single multi-center, randomized, parallel-group, double-blind, phase III study (#ALT 0347-05-01) to determine the safety and efficacy of the new 0.8% Terconazole vaginal cream formulation compared to Terazol[®]3, administered at bedtime for 3 days. A total of 460 female subjects ≥ 18 years with symptoms of VVC and presence of hyphae/pseudohyphae or budding yeast in KOH wet mount preparations of vaginal swab specimen were enrolled. For subjects with a positive KOH, a swab specimen from the vaginal mucosa was used to inoculate the _____ transport tube kit and sent to the central laboratory (_____) for culturing. _____ dextrose agar with and without chloramphenicol plus cyclohexamide was used for isolation of yeast. The isolates were then tested for germ tube formation by incubating the isolates with _____ at 37°C for 4 hours.

Isolates that were positive for germ tube were identified as *Candida albicans*. All other isolates were reported as other *Candida* species. No additional tests were performed to speciate the isolates.

A wet smear of the vaginal swab was prepared for microscopic examination for *Trichomonas vaginalis* and clue cells at baseline. Additionally, a swab specimen was sent to a central reference laboratory to test for presence of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* using a DNA probe assay. Presence of either of these pathogens or clue cells excluded patients from participation in study. Patients with cervical neoplasia or vulvovaginal/genital infections due to herpes simplex or human papilloma virus were excluded. Patients receiving other antifungal or antimicrobial therapies or having allergic reactions to imidazole class of drugs were also excluded. For additional details on the study design, please see Medical Officer's review.

The patients were evaluated for clinical and microbiologic outcomes, at baseline, 5 to 7 days, and 18 to 27 days, after discontinuation of treatment. The primary efficacy endpoint was therapeutic cure (clinical cure and microbiological cure) at 18 to 27 days after discontinuation of treatment. Microbiological cure was based on negative culture for *Candida* species. The secondary efficacy endpoints evaluated the clinical and mycological cure rates, separately.

The modified intent-to-treat (MITT) and per-protocol (PP) populations were analyzed. Of the 485 patients enrolled, 293 (new terconazole product arm, n = 140; Terazol[®]3 arm, n = 153) met the inclusion and exclusion criteria and had a positive culture for *Candida* at baseline and were part of the MITT population. Of the 293 patients, 236 (new terconazole product arm, n = 114; Terazol[®]3 arm, n = 122) were included in the PP analysis. The PP population included MITT patients who complied with 3 days of treatment and had a mycological evaluation at 18 to 27 days after discontinuation of therapy. The clinical and mycological outcomes of patients at 18 to 27 days after discontinuation of therapy stratified by their baseline pathogen are shown in Table 1. The majority of baseline infections were due to *C. albicans* (new terconazole product arm, n = 105; Terazol[®]3 arm, n = 108). The percentage of patients with resolution of VVC symptoms and eradication of baseline *C. albicans* in the new terconazole product arm (76%) was higher than the Terazol[®]3 arm (63%). Few patients were infected with *Candida* species other than *C. albicans* (new terconazole product arm, n = 9; Terazol[®]3 arm, n = 14). Resolution of VVC symptoms and eradication of baseline *Candida* species was observed in 33.3% (3/9) patients treated with the new terconazole product and 36% (5/14) patients treated with Terazol[®]3. Of the 114 patients treated with the new terconazole product, 12 showed a successful clinical and mycological outcome at 5 to 7 days after therapy but relapsed at 18 to 27 days after discontinuation of therapy. Similarly, 14 of the 122 patients treated with Terazol[®]3 showed a successful clinical and mycological outcome at 5 to 7 days after therapy but relapsed at 18 to 27 days after discontinuation of therapy. *In vitro* susceptibility testing of isolates collected at baseline and at 18 to 27 days after discontinuation of treatment was not performed.

Eleven patients (5 in the new terconazole product arm and 6 in the Terazol[®] 3 arm) had new infections at the test-of-cure visit due to a pathogen different from that identified at baseline (Table 2).

Table 1: The clinical and mycological outcome of patients with VVC stratified by baseline pathogen at 18 to 27 days after discontinuation of therapy.

Baseline pathogen and outcome	New Terconazole (0.8%) product		Terazole® 3	
	MITT population (n = 140)	PP population (n = 114)	MITT population (n = 153)	PP population (n = 122)
<i>C. albicans</i>	126	105	137	108
Clinical and mycological cure	96 (76%)	80 (76%)	81 (59%)	68 (63%)
Clinical cure and mycological failure	12 (9.5%)	10 (9.5%)	18 (13%)	15 (14%)
Clinical failure and mycological cure	7 (5.5%)	5 (5%)	8 (6%)	4 (4%)
Clinical and mycological failure	10 (8%)	10 (9.5%)	26 (19%)	20 (18%)
No evaluation	1 (1%)	0 (0%)	4 (3%)	1 (1%)
<i>Candida</i> species	14	9	16	14
Clinical and mycological cure	4 (29%)	3 (33.3%)	5 (31%)	5 (36%)
Clinical cure and mycological failure	3 (21%)	3 (33.3%)	2 (12.5%)	2 (14%)
Clinical failure and mycological cure	1 (7%)	0 (0%)	2 (12.5%)	2 (14%)
Clinical and mycological failure	4 (29%)	3 (33.3%)	7 (44%)	5 (36%)
No evaluation	2 (14%)	0 (0%)	0 (0%)	0 (0%)

Table 2: Patients with new infections in study #ALT 0347-05-01.

Patient ID	Treatment arm	Baseline pathogen [#]	New pathogen at post-treatment visits*
147	New Terconazole (0.8%) product	<i>Candida</i> species	<i>C. albicans</i>
200	New Terconazole (0.8%) product	<i>Candida</i> species	<i>C. albicans</i>
495	New Terconazole (0.8%) product	<i>Candida</i> species	<i>C. albicans</i>
385	New Terconazole (0.8%) product	<i>C. albicans</i>	<i>Candida</i> species
511	New Terconazole (0.8%) product	<i>C. albicans</i>	<i>Candida</i> species
346	Terazole® 3	<i>C. albicans</i>	<i>Candida</i> species
381	Terazole® 3	<i>C. albicans</i>	<i>Candida</i> species
491	Terazole® 3	<i>C. albicans</i>	<i>Candida</i> species
517	Terazole® 3	<i>C. albicans</i>	<i>Candida</i> species
548	Terazole® 3	<i>Candida</i> species	<i>C. albicans</i>
659	Terazole® 3	<i>Candida</i> species	<i>C. albicans</i>

[#] Isolates positive for germ tube were identified as *C. albicans*. All other isolates were reported as *Candida* species.

*post-treatment visits = 5 to 7 days, and 18 to 27 days, after discontinuation of therapy.

5. LABEL:

5.1. Sponsor's proposed label:

Microbiology: Terconazole exhibits fungicidal activity *in vitro* against *Candida albicans*. Antifungal activity has also been demonstrated against other fungi. The MIC values of terconazole against most *Lactobacillus* spp. typically found in the human vagina were ≥ 128 mcg/mL; therefore these beneficial bacteria were not affected by drug treatment.

The exact pharmacologic mode of action of terconazole is uncertain; however, it may exert its antifungal activity by the disruption of normal fungal cell membrane permeability. No resistance to terconazole has developed during successive passages of *C. albicans*.

INDICATIONS AND USAGE

Terconazole vaginal cream 0.8% is indicated for the local treatment of vulvovaginal candidiasis (moniliasis). As these products are effective only for vulvovaginitis caused by the genus *Candida*, the diagnosis should be confirmed by KOH smears and/or cultures.

5.2. Comments:

There are no changes to the microbiology section of the label.

6. CONCLUSIONS:

The applicant developed a new formulation of terconazole 0.8% vaginal cream for the treatment of vulvovaginal candidiasis (VVC). Terazol[®]3 contains 0.8% terconazole and is approved for the treatment of VVC.

The support for the preclinical microbiology aspects of the application is based on the approved label for Terazol[®]3 vaginal cream. The mechanism of action of terconazole is believed to be due to disruption of cell permeability function. *In vitro*, terconazole is active against *Candida albicans* and other fungi. Against *Lactobacillus* species, the terconazole MICs were ≥ 128 $\mu\text{g/ml}$.

The sponsor conducted a single multi-center, randomized, parallel-group, double-blind, phase III study (#ALT 0347-05-01) to determine the safety and efficacy of the new 0.8% Terconazole vaginal cream formulation compared to Terazol[®]3 (0.8% vaginal cream), administered at bedtime for 3 days. The germ tube assay was used to classify the baseline yeast isolate from patients in this study as "*C. albicans*" or "*Candida* species". No additional tests were performed to speciate the isolates. The VVC infection in a majority of patients was due to *C. albicans*. The relapse rate was 11% in both treatment arms. *In vitro* susceptibility testing of isolates collected at baseline and post-treatment was not performed. New infections due to a *Candida* species other than the one observed at baseline was observed in 11 patients (new terconazole product arm = 5; Terazol[®]3 arm = 6). Overall, the results of the study showed that the clinical and mycological outcome of the new terconazole 0.8% vaginal cream product was better than Terazol[®]3.

7. RECOMMENDATIONS:

This NDA is recommended for approval with respect to Microbiology. There are no changes to the microbiology section of the label.

Kalavati Suvarna
Microbiologist, HFD-590

Terconazole

Altana, Inc.

CONCURRENCES:

HFD-590/Deputy Dir	_____	Signature	_____	Date	_____
HFD-590/Micro TL	_____	Signature	_____	Date	_____

CC:

HFD-590/Original IND

HFD-590/Division File

HFD-590/MO

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HFD-590/Chem

HFD-590/Review Micro

HFD-590/CSO/YuYon

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/s/

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