

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-735**

**CHEMISTRY REVIEW(S)**



**NDA 21-735**

**Terconazole Vaginal Cream, 0.8%**

**Altana, Inc.**

**Dorota Matecka  
Division of Special Pathogen and Immunologic Drug  
Products, HFD-590**



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# Chemistry Review Data Sheet

1. NDA 21-735
2. REVIEW #: 1
3. REVIEW DATE: 30-Sept-2004
4. REVIEWER: Dorota Matecka
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	25-Nov-2003
IR	3-Sep-2004
BC	15-Sep-2004
IR	15-Sep-2004
BC	24-Sep-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	25-Nov-2003
BC	15-Sep-2004
BC	24-sep-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Altana, Inc.
Address:	60 Baylis Road Melville, New York 11747
Representative:	Ms. Audrey Zaweski
Telephone:	631-454-7677 x3007
FAX:	631-756-5114



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): terconazole vaginal cream
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505b(2)

10. PHARMACOL. CATEGORY: Antifungal

11. DOSAGE FORM: Vaginal cream

12. STRENGTH/POTENCY: 0.8%

13. ROUTE OF ADMINISTRATION: Vaginal

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

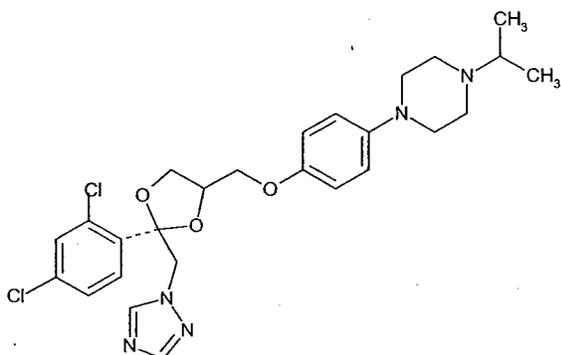
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,  
MOLECULAR WEIGHT

*cis*-(±)-1-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-(1-methylethyl)piperazine

CAS-67915-31-5; C<sub>26</sub>H<sub>31</sub>Cl<sub>2</sub>N<sub>5</sub>O<sub>3</sub>, MW=532.47

## Chemistry Review Data Sheet


**17. RELATED/SUPPORTING DOCUMENTS:**
**A. DMFs:**

DMF #	Type	Holder	Item referenced	Code <sup>1</sup>	Status <sup>2</sup>	Date review completed	Comments
1	II	/	/	1	Adequate	24-Sep-2004	
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	III			3	Adequate	14-Apr-1994	
	III			4	N/A	N/A	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ANDA	✓ 76-712	Terconazole Vaginal Cream, 0.4%
NDA	✓ 19-964	TERAZOL 3 (terconazole) Vaginal Cream, 0.8%

### 18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	28-Apr-2004	Janine D. Ambrogio
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	N/A		
Microbiology	N/A		



# The Chemistry Review for NDA 21-735

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Terconazole Vaginal Cream, 0.8% is identical in components and very similar in composition to a commercially available TERAZOL 3 (terconazole) Vaginal Cream, 0.8%, owned by Johnson & Johnson Pharmaceutical Research & Development, L.L.C, and approved via NDA 19-964 on 21-Feb-1991.

The application for the current product, Terconazole Vaginal Cream, 0.8%, was initially filed with the Office of Generic Drugs (OGD) but it was rejected by OGD because the proposed drug demonstrated a slight improvement over the RLD (Reference Listed Drug; TERAZOL 3 Vaginal Cream) with a confidence interval just outside the range of 80-120% required to demonstrate bioequivalence. Consequently, the applicant has filed an application with the Office of New Drugs (OND) for this product (current NDA 21-735).

It should be noted that the applicant (Altana) has another pending generic application (ANDA 76-712) for a similar product, Terconazole Vaginal Cream, 0.4%, which has a lower strength but identical composition to the current product (0.8% cream). The latest chemistry review (review # 3) of ANDA 76-712 (terconazole vaginal cream, 0.4%) dated 8-Jul-2004 obtained from the OGD reviewer (Dr. Ram Randad) listed two remaining deficiencies: inadequate DMF for terconazole drug substance, and pending bio-equivalency review. All other previously identified CMC issues (via reviews # 1 and # 2) were resolved with the applicant. Therefore, the review # 3 of ANDA 76-712 was used as a reference in the review of the information for terconazole vaginal cream 0.8%, submitted in the current NDA.

**Executive Summary Section**

The drug product, terconazole vaginal cream, 0.8%, is white to off-white, smooth, and homogeneous cream, formulated for topical (vaginal) application and packaged in 20-gram aluminum tubes.

Terconazole drug substance is listed in the British Pharmacopoeia but is not listed in the USP. The manufacturer of terconazole drug substance used by the NDA applicant is \_\_\_\_\_ . For the majority of chemistry, manufacturing and controls (CMC) information regarding \_\_\_\_\_ the reference is made to DMF Type II held by \_\_\_\_\_ Inc.

Terconazole drug substance is a white or almost white powder. It is practically insoluble in water, freely soluble in methylene chloride, acetone and sparingly soluble in alcohol. Terconazole drug substance is used in the Altana's terconazole vaginal cream formulation with a particle size acceptance criterion of \_\_\_\_\_. Terconazole drug substance appears in \_\_\_\_\_ is produced in the drug substance manufacturing process. The identity of terconazole \_\_\_\_\_ in the drug substance specification is confirmed by Differential Scanning Calorimetry (DSC).

The retest period for the terconazole drug substance : \_\_\_\_\_

**B. Description of How the Drug Product is Intended to be Used**

Terconazole Vaginal Cream, 0.8% is indicated for the local treatment of vulvovaginal candidiasis (VVC).

Terconazole Vaginal Cream, 0.8% is supplied in 20 g tube [NDC 0168-0347-20] with one measured dose, reusable, plastic applicator.

One full applicator (5-gram) of terconazole vaginal cream, 0.8% should be administered intravaginally once daily at bedtime for three consecutive days.

The storage conditions statement recommends the following storage: "store at 20-25°C (68-77°F) [see USP controlled Room Temperature]". The expiration dating for the product is 24 months.

**C. Basis for Approvability or Not-Approval Recommendation**

The NDA submission and amendments provide adequate information on the chemistry, manufacturing and controls for the production of terconazole vaginal cream, 0.8%. During the review several minor issues, including the following were resolved.

The proposed specification for the drug product was compared to the specification of the original drug, TERAZOL 3 Vaginal Cream, 0.8%. However, some revisions were made in the specification of Altana's terconazole vaginal cream, 0.8% during the course of the review. Specifically, a second identity test was added. Also, the acceptance criteria for impurities in the drug product were revised to list specified and unspecified impurities. In addition, the acceptance criteria for microbial limits were revised to include the limit for total combined \_\_\_\_\_

**Executive Summary Section**

The stability data submitted in the application (including the 24-Sep-2004 amendment) include — months of data of storage under the room temperature conditions and — months of data at the accelerated conditions for only one batch of the drug product (about — smaller than the production batch). However, considering the fact that this product is identical in components and very similar in composition to an existing product of a known stability profile, the proposed expiration dating (of 24 months) seems to be justified based on the data analysis. It should be noted that the expiration date for the original terconazole vaginal cream, 0.8% (TERAZOL 3 Vaginal Cream) is also 24 months.

No trade name was proposed for this product. The proposed labeling for Terconazole Vaginal Cream, 0.8% is very similar to the labeling of the approved TERAZOL 3 (terconazole) Vaginal Cream, 0.8%.

**III. Administrative****A. Reviewer's Signature**

DFS

**B. Endorsement Block**

ChemistName/Date: Dorota Matecka  
ChemistryTeamLeaderName/Date: Mark Seggel  
ProjectManagerName/Date: Yon Yu

**C. CC Block**

25 Page(s) Withheld

8 § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-

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/s/

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Dorota Matecka  
9/30/04 04:05:08 PM  
CHEMIST

Mark Seggel  
9/30/04 04:12:04 PM  
CHEMIST