CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-806

CHEMISTRY REVIEW(S)

NDA 21-806

Metronidazole Vaginal Gel, 0.75%

TEVA Pharmaceuticals USA

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

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-806

2. REVIEW #: 1

3. REVIEW DATE: 18-May-2005

4. REVIEWER: Dorota Matecka

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	19-July-2004
Filing Notification Letter	15-Sep-2004
C	5-Oct-2004
BC	8-Nov-2004
IR (e-mail)	27-Dec-2004
BZ	3-Feb-2005
IR	28-Feb-2005
BC	27-Apr-2005
IR (e-mail)	5-May-2005
BC	17-May-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	19-July-2004
C	5-Oct-2004
BC	8-Nov-2004
BZ	3-Feb-2005
BC	27-Apr-2005
BC	17-May-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	TEVA Pharmaceuticals USA
Address:	1090 Horsham Road, PO Box 1090 North Wales, PA 1954-1090
Representative:	Vincent Andolina, Director, Regulatory Affairs, Liquid's, Semi-Solids, and Specialty Projects
Telephone:	(215) 591-3000

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:
b) Non-Proprietary Name (USAN):
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 0.75% w/w

13. ROUTE OF ADMINISTRATION: Vaginal

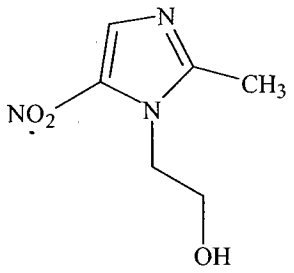
14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

2-methyl-5-nitroimidazole-1-ethanol
CAS 443-48-1; MW = 171.15; $C_6H_9N_3O_3$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	Metronidazole	1	Adequate	10-Oct-2004	N/A
[redacted]	III	[redacted]	[redacted]	4	N/A	N/A	N/A
[redacted]	III	[redacted]	[redacted]	3	Adequate	14-Apr-1994	N/A
[redacted]	III	[redacted]	[redacted]	4	N/A	N/A	N/A
[redacted]	III	[redacted]	[redacted]	4	N/A	N/A	N/A
[redacted]	III	[redacted]	[redacted]	4	N/A	N/A	N/A

[1] 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")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-208	MetroGel-Vaginal, 0.75%

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	13-Sep-2004	Janine D. Ambrogio
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	Acceptable	24-Feb-2005	Guirag Poochikian, Ph.D.
Methods Validation	N/A		
DMETS	N/A		
EA	N/A (EA exemption)		
Microbiology	N/A		

The Chemistry Review for NDA 21-806

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)

The drug product, Metronidazole Vaginal Gel, 0.75%, is a colorless to yellow, clear and homogeneous gel, formulated for topical (vaginal) application and packaged in 70-gram aluminum tubes.

Metronidazole Vaginal Gel, 0.75%, is very similar in components and composition to a commercially available MetroGel-Vaginal® (metronidazole vaginal gel) Vaginal Gel, 0.75%, owned by 3M Pharmaceuticals, and approved via NDA 20-208 on 17-Aug-1992. The difference in the components/composition between these two products includes the presence of [redacted] of Hypromellose (hydroxypropyl methylcellulose) in the TEVA's gel versus [redacted] of Carbomer 934 [redacted] present in MetroGel-Vaginal® of 3M Pharmaceuticals. The most significant difference in the properties of the two gels includes the pH value, i.e. 4.0-6.5 versus 3.6-4.2 for the TEVA'a gel and 3M Pharmaceuticals' gel, respectively. With respect to the other physico-chemical and rheological properties of the gels, i.e. specific [redacted] the differences were less significant, as indicated by the testing of both gels using the same analytical procedures and conditions, which was conducted by the applicant in response to the Agency's request.

The application for the current product, Metronidazole Vaginal Gel, 0.75%, was initially submitted the Office of Generic Drugs (OGD) but it was rejected by OGD because the proposed drug product demonstrated a slight improvement over the RLD (Reference Listed Drug; MetroGel-Vaginal®) with a confidence interval just outside the range required to demonstrate bioequivalence. Consequently, the applicant has filed the current application (NDA 21-806) with the Office of New Drugs (OND).

Each gram of the drug product, Metronidazole Vaginal Gel, 0.75%, contains 7.5 mg of metronidazole providing a total dose of 37.5 mg of the drug substance per one application (applicator full of 5 gram of the gel). Metronidazole Vaginal Gel, 0.75%, is not sterile, however, it contains an antimicrobial preservative system consisting of [redacted] of methylparaben and [redacted] of propylparaben per one gram of the gel. The same preservative system is utilized in the 3M Pharmaceuticals' product (MetroGel-Vaginal®). In addition, the proposed drug product specification includes a microbial limits test with appropriate acceptance criteria for a vaginal product, which is conducted annually throughout the shelf life of the product.

The active ingredient of Metronidazole Vaginal Gel, 0.75%, metronidazole, is a member of the imidazole class of antibacterial agents. Metronidazole drug substance appears as pale yellow, odorless crystals or crystalline powder, which is sparingly soluble in water and alcohol, and slightly soluble in ether and chloroform.

Metronidazole drug substance used in the proposed TEVA's product meets the requirements of the USP monograph for Metronidazole. The manufacturer of metronidazole drug substance used by the applicant is [redacted]. It should be noted that 3M Pharmaceuticals [redacted] product, MetroGel-Vaginal®.

For the majority of chemistry, manufacturing and controls (CMC) information regarding the metronidazole drug substance, the reference is made to DMF Type II [redacted]. DMF [redacted] was previously reviewed and found acceptable with reference to other metronidazole [redacted] products (including products for vaginal administration). The latest acceptable review of this DMF is dated 10-Oct-2004.

Each lot of metronidazole received by TEVA Pharmaceuticals USA will be fully tested according to the specification provided in the application. A retest period of one year will be used.

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

Metronidazole Vaginal Gel, 0.75% is indicated for the local treatment of bacterial vaginosis (BV).

Metronidazole Vaginal Gel, 0.75% is supplied in 70-g aluminum tube with five measured dose, disposable, plastic applicators.

The recommended dose is one applicator full of metronidazole vaginal gel, 0.75% (approximately 5 grams of gel containing approximately 37.5 mg of metronidazole) administered intravaginally once or twice daily for five 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 Metronidazole Vaginal Gel, 0.75%. During the review several minor issues, including the following were resolved.

The specification of the drug product, Metronidazole Vaginal Gel, 0.75%, was revised to include the [redacted] analytical procedure and acceptance criteria. Also, the proposed description of the gel was revised to describe more accurately the color of the gel. In addition, the quantitative color analytical procedure and acceptance criteria were added to the drug product specification to provide a better control of the color changes on storage. As mentioned above, the metronidazole drug substance complies with the USP monograph for Metronidazole. However the monograph does not contain a method (HPLC) for chromatographic purity. Therefore, the inclusion of the HPLC analytical procedure and acceptance criteria in the drug substance specification was recommended.

The stability data submitted in the application (including the 27-Apr-2005 amendment) support the proposed expiration dating of 24 months for the drug product. It should be noted that the expiration dating for the original metronidazole vaginal gel (MetroGel-Vaginal®, 0.75%) is 36 months.

No trade name was proposed for this product. The established name was consulted with the Labeling and Nomenclature Committee (LNC). The originally proposed established name for the drug product "Metronidazole Gel USP, 0.75% w/w Vaginal" was found unacceptable for the following reasons. The drug product complies with most of the requirements of the USP monograph for Metronidazole Gel. However, several tests in the specification of the current product are new or different from those listed in the monograph. For example, the TEVA's drug product specification uses a UV, instead of [redacted] as one of the identification tests. The HPLC analytical procedure for assay and impurities is also different than that of the USP monograph. Therefore, the USP designation should not be used for this product and the following established name was recommended: "Metronidazole Vaginal Gel". The word "vaginal" was incorporated in the name to indicate the route of administration

The proposed labeling for Metronidazole Vaginal Gel, 0.75% is similar to the labeling of the approved MetroGel-Vaginal®, 0.75%. Several revisions in both, labeling (e.g. the description section) and the carton label, were recommended and adopted by the applicant.

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

29 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dorota Matecka
5/19/05 03:29:08 PM
CHEMIST

Mark Seggel
5/19/05 03:59:02 PM
CHEMIST