CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-014

CHEMISTRY REVIEW(S)

Memorandum

Date: July 24, 2007
From: Zhengfang Ge, Ph.D., Reviewer
Through: Moo Jhong Rhee, Ph.D., Branch Chief
To: NDA 22-014
Subject: Addendum to Review #1

The sponsor submitted the final revised container labels in an amendment dated July 17, 2007 per Agency's comments. As indicated in the Review #1 (pp 56-58), the revised container labels are acceptable. From CMC point of view, this NDA can be approved.

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

/s/

Zhengfang Ge
7/24/2007 04:04:35 PM
CHEMIST

Moo-Jhong Rhee
7/24/2007 04:12:16 PM
CHEMIST
Chief, Branch III

NDA 22-014

EvaMist (Estradiol Transdermal Spray), 1.7% w/v
Vivus, Inc

Division of Reproductive and Urologic Products

Zhengfang Ge, Ph.D.

Branch III, Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA # 22-014

2. REVIEW # 1

3. REVIEW DATE: July 18, 2007

4. REVIEWER: Zhengfang Ge

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	Sep 29, 2006
Amendment (N000_C)	Dec 20, 2006
Amendment (N000_BC)	Jan 30, 2007
Amendment (N000_BM)	April 25, 2007
Amendment	June 18, 2007
Amendment	June 19, 2007

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Vivus, Inc
Address:	1172 Castro Street Mountain View, CA 94040
Representative:	Leland F. Wilson
Telephone:	650-934-5200

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: EvaMist
b) Non-Proprietary Name (USAN): Estradiol
c) CAS No: 50-28-2
d) Code Name/# (ONDQA only): None
e) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: This application was filed under the provisions of section 505(b)(1) of Federal Food, Drug and Cosmetic act and 21 CFR 314.50.

10. PHARMACOL. CATEGORY: Treatment of moderate-to-severe vasomotor symptoms associated with menopause.

11. DOSAGE FORM: Spray

12. STRENGTH/POTENCY: 1.7% w/v, 1.53 mg/spray

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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

Chemistry Review Data Sheet

_____SPOTS product – Form Completed

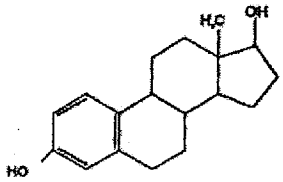
___X__Not a SPOTS product

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

Name:

Estra-1,3,5(10)-triene-3,17-diol, (17ß) or Estra-1,3,5(10)-triene-3, 17ß-diol

Molecular Formula: $C_{18}H_{24}O_2 \cdot 1/2H_2O$



$.1/2H_2O$

Molecular Weight: 281.4

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	II	—	—	3	Adequate	27-Jan-2006	Reviewed by B. Cai, Ph.D. for ANDA 75-182
—		—	—	7	N/A		Complies to USP
—	III	—	—	3	Adequate		01-Mar-1996 for NDA — by H. Patel
—	III	—	—	4	N/A		Sufficient information in this NDA
—	III	—	—	4	N/A		Sufficient information in this NDA

b(4)

[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

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Acceptable	08-Nov-2006	Office of Compliance
Pharm/Tox	see review for container/closure		Leslie McKinney
Biopharm	not applicable		
LNC	Not Applicable		
Methods Validation	post approval		
DMETS	see review for labeling		
EA	Adequate		Section II/B of this review
Microbiology	Not applicable		

The Chemistry Review for NDA 22-014

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The sponsor has provided adequate resolution for all the CMC issues found during the review. From CMC point of view, this NDA can be approved.

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

None

II. Summary of Chemistry Assessments

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

Drug Substance:
The drug substance is Estradiol with a molecular formula of $C_{18}H_{24}O_2 \cdot 1/2H_2O$ and molecular weight of 281.4. The manufacturer of the drug substance is the same one for NDA 21-813 (Elestrin, 0.06% estradiol gel), which is also reviewed by this reviewer. The sponsor for this NDA also cross-referenced DMF for related CMC information of the drug substance. An authorization letter was provided in this application. The DMF was reviewed on 27-Jan-2006 by Dr. B. Cai and was found adequate for ANDA 75-182. No updated information was submitted to the DMF after the review. The sponsor provided an adequate acceptance specification and Certification of Analysis for the drug substance. The manufacturing facility is inspected with an "Acceptable" recommendation from the Office of Compliance.

Drug Product:
The drug product is an estradiol transdermal spray. Each actuation delivers 90 µl of spray, containing 1.53 mg estradiol. The daily dose is 1-3 sprays/day. The drug product is a single-phase solution of estradiol (1.7% w/v) and a penetration enhancer (octisalate — in alcohol. The estradiol solution is filled into a — glass vial with a — Each vial contains 8.1 ml of solution and is closed with a — topped with a — b(4)
Each container is designed to deliver 56 dose of sprays (5.04 ml), leaving approximately 3 ml of solution in the container after labeled use. The glass vial is encased in a — with a conical bell opening that controls the distance, angle, and area of the metered-dose spray.

The manufacturing process is [redacted] b(4)

The main challenge for this product is the container closure system and the spray quality. The sponsor provided sufficient information regarding the container/closure system in this NDA. Test results for extractable/leachable of the container/closure are reviewed and are acceptable, concurred by PharmTox reviewer. The sponsor reported that active residue was found to be built up on the nozzle and shroud, but the sponsor explained that the built up would not impact the spray pattern. Based on the content uniformity results, the sponsor's justification is acceptable.

The sponsor proposed a regulatory specification using PTIT (Parametric Tolerance Interval Testing) for the drug product. PTIT is a new statistical approach for the dose content uniformity testing, initiated for the pulmonary drug products. The review of this method is based on Agency's previous experience with the pulmonary products, [redacted] b(4)

The sponsor accepted the Agency's recommendation in the Amendment dated 18-June-2007.

The sponsor provided 18 month long term stability data for 2 batches, 12 months long term stability data for one batch and 6 month accelerated stability data for all three batches of drug product. No change in the estradiol content and no degradation products of estradiol were detected. A slight decrease in octisalate content, particularly in the first 3 months of storage, is detected. Ethanol content remained unchanged during the stability study at all the storage conditions. [redacted] b(4)

[redacted] No change in spray pattern was observed over time. There was a few failures of spray content uniformity at the end of container life, the sponsor provided justification for the failure. Over all, changes in the stability results are not significant. Based on the stability data, the sponsor's proposal of 24 month expiration date is acceptable.

The sponsor provided a comparability protocol for an [redacted] of the drug product container and proposed a CBE 30 supplement for the [redacted] b(4)

[redacted] the container components and metered applicator remain the same. Based on the current stability results, the proposed comparability protocol for the CBE 30 supplement of the [redacted] of the drug products is acceptable.

The manufacturing facility is inspected with an "Acceptable" recommendation from the Office of Compliance.

The sponsor proposed to use (estradiol transdermal spray) as established name, which is acceptable. Some minor modifications for the labeling and container labels were provided during the labeling review. The revised labeling is acceptable from CMC prospective.

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

The drug product is indicated for the treatment of moderate- to-severe vasomotor symptoms. It will be applied 1-3 sprays daily to adjacent non-overlapping (side-by-side) 20 cm^2 areas on the inner surface of the arm between the elbow and wrist and allowed to dry.

C. Basis for Approvability or Not-Approval Recommendation

The CMC information for the drug substance is referenced to DMF — which is found adequate previously. The sponsor has adequately addressed CMC deficiencies listed in review section III. The NDA can be approved from CMC prospective. b(4)

III. Administrative

A. Reviewer's Signature

In DFS

B. Endorsement Block

Chemist: Zhengfang Ge
Chemistry Branch Chief: Moo-Jhong Rhee

C. CC Block

ProjectManager: Kassandra Sherrod
Pharmaceutical Assessment Lead: Danna Christner

55 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/

Zhengfang Ge
7/18/2007 02:06:47 PM
CHEMIST

Moo-Jhong Rhee
7/18/2007 02:16:24 PM
CHEMIST
Chief, Branch III