CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-014

OTHER REVIEW(S)

MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology HFD-420; White Oak BLDG 22, Room 4447 Center for Drug Evaluation and Research

To: Scott Monroe, MD
Acting Director, Division of Reproductive and Urologic Products, HFD-580

Through: Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

From: Todd Bridges, R.Ph., Team Leader
Division of Medication Errors and Technical Support, HFD-420

Date: July 25, 2007

Subject: DMETS Label and Labeling Review
Drug: Evamist
(Estradiol Transdermal Spray)
1.53 mg/spray
NDA #: 22-014
Sponsor: Vivus, Inc.

Review #: 2007-1607

This memorandum is in response to a July 24, 2007, request from the Division of Reproductive and Urologic Products (HFD-580) for a review of the revised container label, carton and insert labeling submitted by the sponsor in response to OSE Review #2006-872, dated June 28, 2007. DMETS acknowledges that the sponsor has addressed all of our label and labeling recommendations. We do not have any additional comments at this time.

If you have questions or need clarifications, please contact Cherye Milburn, OSE Project Manager, at (301) 796-2084.

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/s/

Todd Bridges
7/25/2007 02:53:02 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/25/2007 04:48:41 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 12, 2007

TO: Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products

VIA: Kassandra Sherrod, R.Ph., Regulatory Project Manager
Division of Reproductive and Urologic Drug Products

FROM: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Deputy Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review of Patient Labeling for TRADE NAME (estradiol transdermal spray), NDA 22-014

See the attached patient labeling (PPI) for our recommended revisions to the required draft PPI submitted for TRADE NAME (estradiol transdermal spray), ND[redacted] These revisions are based on draft professional labeling submitted in SPL format on September 28, 2006. It is noted that a trade name review by DMETS is pending at this time, for the sponsor's proposed trade name EvaMist. b(4)

Comments and Recommendations

1. A PPI is required for this drug product. We have made it consistent with the November 2005 (Revision 4) *Draft Guidance for Industry: Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Prescribing Information for Health Care Providers and Patient Labeling*, based on the WHI study.
2. The sponsor has provided a Word file of the draft PPI for our review, which does not contain the illustrations submitted in the original paper submission for this NDA. Therefore, our review and comments focus on the language in the PPI. The PPI must always be consistent with the PI.
3. According to *21 CFR 201.57 (c) (18) 17 Patient Counseling Information, "This section must contain information necessary for patients to use the drug safely and effectively (e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects). Any FDA-approved patient labeling must be referenced in this section and the full text of such patient labeling must be reprinted immediately following this section or alternatively, accompany the prescription drug labeling.*"

   Section 2.0, Dosage and Administration, and Section 17, *Patient Counseling,* should be expanded. The sponsor proposes language advising physicians to discuss the contents of

the Patient Information leaflet with patients for whom they prescribe TRADE NAME; however, much of the proposed information in the PPI under the sections "How should I use TRADE NAME"and the "Patient Instructions for Use" does not appear in the PI. The following information should be added to the PI to instruct healthcare providers in how to counsel patients regarding use of TRADE NAME:

- Apply TRADE NAME to clean, dry, unbroken skin
- Do not apply TRADE NAME directly to the breast.
- Do not allow others to make contact with the area of skin where you applied the spray for at least 30 minutes after application.
- If you miss a dose of TRADE NAME, do not double the dose on the next day to catch up. If your next dose is less than 12 hours away, it is best just to wait and apply your normal dose the next day. If it is more than 12 hours until the next dose, apply the dose you missed and go back to your normal dosing the next day.
- **TRADE NAME contains alcohol. Alcohol based liquids are flammable. Avoid fire, flames or smoking when using TRADE NAME until the spray has dried. Do not apply TRADE NAME while standing near a flame.**
- If a 2 or 3 spray dose is prescribed by your healthcare provider, apply the extra doses by moving the cone to another area of the skin next to the area that you just sprayed. Allow room in-between so that the doses do not go on top of one another (overlap) (see illustration #4).
- b(4)
- Always place the protective cover back on the cone of the applicator when you are finished taking your daily dose of TRADE NAME.
- Do not massage or rub TRADE NAME into the skin. Allow the spray to dry for at least 2 minutes before dressing, and at least 30 minutes before washing.

4. The order in which the inactive ingredients are listed in the PI differs between section 11.0 *Description* and Section 16.0 *How Supplied/Storage and Handling. Alcohol USP is listed before octisalate USP in section 11.0; however, it is listed after octisalate USP in section 16.0. Consider making these two sections consistent.*
5. We recommend that the "Patient Instructions for Use" be moved to the end of the Patient Information leaflet to be consistent with other patient labeling materials.
6. All future changes to the PPI must be consistent with the PI.

Comments to the review division are ***bolded, underlined and italicized***. Attached to the memo we are providing to the review division a marked-up and clean copy of the revised PPI in Word. We recommend using the clean copy as the working document.

Please call us if you have any questions.

APPEARS THIS WAY ON ORIGINAL

17 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Others 1

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/s/

Sharon Mills
2/12/2007 03:02:27 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
2/12/2007 04:19:27 PM
DRUG SAFETY OFFICE REVIEWER