CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-014

SUMMARY REVIEW

DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS (DRUP)
DIVISION DIRECTOR MEMORANDUM

NDA	NDA 22-014
Type of Application	Original
Applicant	VIVUS, Inc. Mountain View, CA
Proprietary Drug Name	Evamist
Established Drug Name	Estradiol transdermal spray
Drug Class	Estrogen
Indications	Treatment of moderate to severe vasomotor symptoms due to menopause
Route of administration	Topical (transdermal)
Dosage Form	Transdermal spray; each 90 µl spray delivers 1.53 mg estradiol
Dosing Regimen	One, two, or three sprays applied each morning to adjacent, non-overlapping areas on the inner surface of the forearm. Therapy should be initiated with one spray per day. Dosing may be increase to two or three sprays per day depending on the clinical response.
PDUFA Goal Date	July 29, 2007
Date of Memorandum	July 27, 2007
Division Director	Scott E. Monroe, MD Acting Division Director, DRUP

1. RECOMMENDATIONS

1.1 Recommendation regarding Approvability

I concur with the primary Medical Reviewer and the Clinical Team Leader that Evamist (estradiol transdermal spray) administered as 1, 2, or 3 sprays to adjacent areas of the forearm in the morning, be approved for the indication of "treatment of moderate to severe vasomotor symptoms due to menopause."

1.2 Basis for Recommendation regarding Approvability

The Applicant has demonstrated in a single, adequate, randomized, double-blind, placebo-controlled clinical trial that each of 3 dose levels of Evamist (1, 2, or 3 sprays) administered once daily was statistically and clinically superior to placebo in terms of reducing the frequency of moderate to severe hot flushes. Each of the 3 dose levels of Evamist also was statistically superior to placebo in terms of reducing the severity of hot flushes. The safety profile for each dose level of Evamist was acceptable for an estrogen drug product for the treatment of moderate to severe vasomotor symptoms (VMS) associated with the menopause.

1.3 Recommendation on Risk Management Steps and/or Phase 4 Studies

1.3.1 Recommendation on Risk Management Steps

No postmarketing risk management steps, other than standard class labeling for an estrogen drug product, are required or requested.

1.3.2 Phase 4 Studies

No Phase 4 studies are required.

2. PRODUCT DESCRIPTION

Evamist (estradiol transdermal spray) is a metered dose transdermal spray (MDTS) of estradiol. Evamist contains a homogeneous solution of 1.7% estradiol (USP) and — octisalate (USP) in — alcohol (USP) formulated to provide a sustained delivery of estradiol into the systemic circulation. The metered dose pump delivers 90 µl (1.53 mg of estradiol) per actuation. b(4)

3. REVIEW ISSUES

The only significant review issue concerned whether the 3-spray dosage of Evamist should be approved. Although efficacy was demonstrated in all 3 dosage groups, the study results showed little clinical difference between the 2-spray dose and the 3-spray dose. This finding was consistent with the pharmacokinetic data, which also showed little difference in the C_{max} and $C_{average}$ values for the 2-spray and 3-spray doses as measured on Day 14 in the primary pharmacokinetic study. The design of the spray cone delivery system for Evamist and potential variability of delivery of the spray to the forearm of women may be responsible for the lack of dose proportionality. In women with a small forearm, a portion of the spray might not contact the surface of the forearm, and thus will not be absorbed. Nevertheless, treatment with all 3 of the dosages demonstrated efficacious and safe results.

Both the primary Medical Reviewer and the Clinical Team Leader have recommended approval of all 3 doses of Evamist (i.e., 1, 2, and 3 sprays). The Clinical Team Leader states the following in her review: *"It is this reviewer's belief that even though the mean treatment data did not demonstrate better results with the 3-spray dose than with the 2-spray dose in the primary clinical trial, in actual market use, some individual women may receive benefit from the 3-spray dose beyond that of the 2-spray dose and, thus, all 3 efficacious and safe doses should be available to titrate the dosage if necessary."*

Division Director's Comments

- *I concur with the recommendations of the primary Medical Reviewer and the Clinical Team Leader and will approve all 3 doses (i.e., 1, 2, and 3 sprays) of Evamist.*
- *The Division has long considered that multiple doses of estrogen products, which meet the criteria for safety and efficacy, should be available to allow for dose escalation in individual patients who do not obtain acceptable relief from a lower dose. Labeling for Evamist states the following: "Evamist therapy should be initiated with one spray. Dosage adjustment should be guided by the clinical response."*

- *The Sponsor will be encouraged to study post-approval the effectiveness and dose proportionality of Evamist when applied to a site other then the forearm, such as the thigh.*

4. CLINICAL PROGRAM

4.1 Overview

The clinical program for Evamist included one adequate and well-controlled Phase 3 trial (Study EST-01) and 3 pharmacokinetic studies. The primary source of efficacy and safety data for Evamist was Study EST-01.

4.2 Primary Efficacy and Safety Clinical Trial (Study EST-01)

Study EST-01 was a Phase 3 multicenter (43 sites in the US), randomized, double-blind, parallel group, and placebo-controlled trial. The study was conducted in accordance with the recommendations of the January 2003 draft Guidance for Industry, entitled "Estrogen and Estrogen/Progestin Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" (hereafter referred to as the HT Guidance).

Only potential subjects who had ≥ 8 moderate-to-severe hot flushes per day at baseline and met other entry criteria consistent with the HT Guidance were enrolled. Subjects were randomized to receive 1, 2, or 3 transdermal sprays of estradiol, or matching placebo, once daily for 12 weeks. A total of 454 subjects received at least one dose of the test material and were analyzed in the intent-to-treat population (ITT).

4.3 Subject Disposition in Study EST-01

The disposition of subjects in Study EST-01 is shown in Table 1.

Table 1 Disposition of Subjects in Study EST-01

	Estradiol 1-spray	Placebo 1-spray	Estradiol 2-spray	Placebo 2-spray	Estradiol 3-spray	Placebo 3-spray
Randomized	77	77	76	76	76	76
Randomized and Used Test Article (ITT)*	76 (98.7)	77 (100.0)	74 (97.4)	76 (100.0)	76 (100.0)	75 (98.7)
Completed Study*	68 (88.3)	58 (75.3)	61 (80.2)	64 (84.2)	69 (90.8)	57 (75.0)
Discontinuations** n (%)	8 (10.5)	19 (24.7)	13 (17.6)	12 (15.8)	7 (9.2)	18 (24.0)
Discontinued Due to:						
Adverse Event[1] n (%)	*2 (25.0)*	*2 (10.5)*	*2 (15.4)*	*3 (25.0)*	*2 (28.6)*	*1 (5.6)*
Hurricane[2]	*1 (12.5)*	*3 (15.8)*	*3 (23.1)*	*2 (16.7)*	*0*	*4 (22.2)*
Lost to Follow-up	*1 (12.5)*	*1 (5.3)*	*4 (30.8)*	*1 (8.3)*	*2 (28.6)*	*4 (22.2)*
Compliance	*1 (12.5)*	*3 (15.8)*	*1 (7.7)*	*0*	*0*	*0*
Subject Request	*3 (37.5)*	*9 (47.4)*	*2 (15.4)*	*4 (33.3)*	*2 (28.6)*	*7 (38.9)*
Other	*0*	*1 (5.3)*	*1 (7.7)*	*2 (16.7)*	*1 (14.3)*	*2 (11.1)*

Source:Figure 2 on page 54, disposition description on page 55, and Table 7 on page 63 of Study EST-01 report.
* With respect to number of randomized subjects
** With respect to number of ITT subjects.
[1] With respect to number of discontinuations
[2] Subject discontinued due to Hurricane Katrina event

Source: Table 3.3, FDA Statistical Review.

Division Director's Comments

- *There was no correlation between the daily dose of Evamist and the percentage of subjects who terminated prematurely for any reason or the percentage of subjects who terminated because of an adverse event.*

5. EFFICACY

5.1 Primary Efficacy Endpoint and Efficacy Analysis

The primary efficacy analysis was based on the reduction from baseline in the frequency and severity of hot flushes in the Evamist treatment groups, compared to that in the respective placebo groups. In accordance with the HT Guidance, the times of primary interest were treatment Week 4 and Week 12.

5.2 Primary Efficacy Findings

The mean daily number of moderate-to-severe hot flushes and the change from baseline in each of the treatment groups at Week 4 and Week 12 is shown in Table 2. In each of the 3 estradiol treatment groups, the reduction from baseline in the mean daily number of hot flushes at Week 4 and Week 12 was statistically greater than that in the respective placebo group.

Table 2 Mean Daily Number of Moderate-to-Severe Hot Flushes and Change from Baseline (Intent-to-Treat Population with Last Observation Carried Forward [LOCF])

Week	1 Spray Estradiol N = 76	1 Spray Placebo N =77	2 Sprays Estradiol N = 74	2 Sprays Placebo N = 76	3 Sprays Estradiol N = 76	3 Sprays Placebo N =75
Baseline						
Mean Number	11.81	12.41	12.66	12.13	10.78	12.55
Week 4						
Mean Number	5.55	8.77	5.36	7.39	4.14	8.01
Mean Change	-6.26	-3.64	-7.30	-4.74	-6.64	-4.54
p-value vs. placebo	0.0010		0.0027		0.0002	
Week 12						
Mean Number	3.71	7.65	4.00	5.94	2.24	7.23
Mean Change	-8.10	-4.76	-8.66	-6.19	-8.44	-5.32
p-value vs. placebo	0.0004		0.0099		<0.0001	

Source: Modified from Table 1 of the Review of the Clinical Team Leader, signed July 27, 2007.

The mean severity of hot flushes and the change from baseline in each of the treatment groups at Week 4, Week 5, and Week 12 is shown in Table 3. In each of the 3 estradiol treatment groups, the reduction from baseline in the mean daily severity of hot flushes at Week 5 and Week 12 was statistically greater than that in the respective placebo group. The reduction from baseline also was statistically greater in the 2-spray and 3-spray estradiol groups, compared to placebo, at Week 4.

Table 3 Mean Severity of Hot Flushes and Change from Baseline (Intent-to-Treat Population with LOCF)

Week	1 Spray Estradiol N = 76	1 Spray Placebo N =77	2 Sprays Estradiol N = 74	2 Sprays Placebo N = 76	3 Sprays Estradiol N = 76	3 Sprays Placebo N =75
Baseline						
Mean Severity	2.53	2.55	2.54	2.54	2.58	2.54
Week 4						
Mean Severity	2.06	2.36	1.97	2.29	2.15	2.41
Mean Change	-0.47	-0.19	-0.57	-0.25	-0.43	-0.13
p-value vs. placebo	0.0573		0.0160		0.0031	
Week 5						
Mean Severity	1.96	2.38	1.91	2.23	1.95	2.36
Mean Change	-0.57	-0.17	-0.63	-0.31	-0.63	-0.18
p-value vs. placebo	0.0034		0.0239		0.0004	
Week 12						
Mean Severity	1.49	2.29	1.62	2.00	1.51	2.23
Mean Change	-1.04	-0.26	-0.92	-0.54	-1.07	-0.31
p-value vs. placebo	<0.0001		0.0406		<0.0001	

Source: Modified from Table 2 of the Review of the Clinical Team Leader, signed July 27, 2007.

Division Director's Comments

- *A reduction of 2 hot flushes/day above that of placebo has been considered by the Division as representing a clinically significant treatment effect. All 3 doses of Evamist produced a reduction of ≥ 2 hot flushes/day above that of placebo treatment.*
- *Although the reduction in the severity of hot flushes did not reach statistical significance (p=0.0573) in the 1-spray estradiol group by Week 4, significance was reached by Week 5 and maintained through Week 12.*

5.3 Overall Assessment of Efficacy

The Applicant has demonstrated in a single, adequate, randomized, double-blind, placebo-controlled clinical trial that each of 3 dose levels of Evamist (1, 2, or 3 sprays) administered once daily was statistically and clinically significantly superior to placebo in terms of reducing the frequency of moderate to severe hot flushes. Each of the 3 dose levels of Evamist also was statistically superior to placebo in terms of reducing the severity of hot flushes.

6. SAFETY FINDINGS

6.1 Safety Database

Safety data from Study EST-01 were combined with data from three Phase 1 pharmacokinetic studies (EST-02, EST-06, and FHRT-06) and were submitted in support of the safety of Evamist. Safety data included data from 454 subjects in Study EST-01 and 71, 20, and 11 subjects in Studies EST-02, EST-06, and FHRT-06, respectively. Two hundred twenty six (226) of the subjects in Study EST-01 and all subjects in the Phase 1 studies were exposed to estradiol transdermal spray. The safety findings from each of the clinical studies, particularly Phase 3 Study EST-01, were thoroughly analyzed in the review of the primary Medical Reviewer.

Division Director's Comment

- *The safety database, although small by usual standards, is adequate for a transdermal estrogen drug product. The adverse events associated with the use of transdermal estradiol for the treatment of VMS are well established.*

6.2 Deaths and Other Serious Adverse Events

Deaths. No deaths were reported to have occurred in any of the clinical trials.

Serious Adverse Events. In Study EST-01, 9 serious adverse events were reported in 8 subjects (7 subjects treated with transdermal estradiol spray and 1 subject receiving placebo). In subjects receiving transdermal estradiol, the events included dyspnea, uterine prolapse, spinal column stenosis, impaired gastric emptying, chest pain (each in a single subject) and exacerbation of chronic obstructive pulmonary disease in 2 subjects. Palpitations and dizziness were reported for a single placebo-treated subject.

Withdrawals due to Adverse Events. Twelve (12) subjects withdrew from the study (6 in the transdermal estradiol spray treatment groups and 6 in the placebo groups) for treatment emergent adverse events. In the transdermal estradiol spray groups, 5 subjects were withdrawn due to adverse events considered related to treatment (ovarian cyst, headache, nipple pain, chest pain, and nausea). In the placebo groups, 3 subjects withdrew due to treatment-related events (increased blood pressure, pruritic rash, vaginal hemorrhage).

Endometrial Hyperplasia. One of the most concerning adverse events commonly associated with use of unopposed estrogens in women with a uterus is endometrial hyperplasia. To address this concern, endometrial biopsies were obtained in a significant percentage of subjects both prior to and at the end of treatment. Among the 75 subjects who received transdermal estrogen and had an end-of-treatment biopsy, one case of simple endometrial hyperplasia (a subject who had received 2 sprays/day) was reported.

Division Director's Comment

- *The types of serious adverse events reported in the clinical trials as well as a single case of simple endometrial hyperplasia do not raise any unique concerns about the safety of Evamist.*

6.3 Common Adverse Events

Adverse events most commonly reported in Study EST-01 are listed in Table 4.

Table 4 Adverse Events Reported in > 1% of Subjects

Event	Frequency n (%)					
	3 Sprays		2 Sprays		1 Spray	
	Estradiol (N = 76)	Placebo (N = 75)	Estradiol (N = 74)	Placebo (N = 76)	Estradiol (N = 76)	Placebo (N = 77)
Infections and Infestations						
Nasopharyngitis	1 (1.3)	1 (1.3)	3 (4.1)	2 (2.6)	4 (5.3)	1 (1.3)
Sinusitis	2 (2.6)	2 (2.7)	2 (2.7)	0 (0.0)	2 (2.6)	1 (1.3)
Urinary Tract Infection	1 (1.3)	1 (1.3)	3 (4.1)	2 (2.6)	1 (1.3)	1 (1.3)
Upper Respiratory Tract Infection	2 (2.6)	0 (0.0)	0 (0.0)	2 (2.6)	1 (1.3)	1 (1.3)
Influenza	1 (1.3)	1 (1.3)	0 (0.0)	2 (2.6)	0 (0.0)	1 (1.3)
Vaginitis Bacterial	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.3)	1 (1.3)	2 (2.6)
Nervous System Disorders						
Headache	8 (10.5)	7 (9.3)	9 (12.2)	5 (6.6)	7 (9.2)	4 (5.2)
Dizziness	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.3)	2 (2.6)	1 (1.3)
Reproductive System and Breast Disorders						
Breast Tenderness	4 (5.3)	0 (0.0)	5 (6.8)	4 (5.3)	4 (5.3)	0 (0.0)
Metrorrhagia	3 (3.9)	1 (1.3)	2 (2.7)	1 (1.3)	2 (2.6)	0 (0.0)
Nipple Pain	1 (1.3)	0 (0.0)	5 (6.8)	0 (0.0)	2 (2.6)	0 (0.0)
Vaginal Hemorrhage	2 (2.6)	2 (2.7)	1 (1.4)	0 (0.0)	0 (0.0)	1 (1.3)
Breast Discoloration	2 (2.6)	0 (0.0)	1 (1.4)	0 (0.0)	2 (2.6)	0 (0.0)
Breast Pain	0 (0.0)	0 (0.0)	2 (2.7)	1 (1.3)	1 (1.3)	1 (1.3)
Gastrointestinal Disorders						
Nausea	2 (2.6)	4 (5.3)	2 (2.7)	1 (1.3)	1 (1.3)	5 (6.5)
Diarrhea	2 (2.6)	0 (0.0)	1 (1.4)	2 (2.6)	0 (0.0)	2 (2.6)
Dyspepsia	2 (2.6)	1 (1.3)	0 (0.0)	1 (1.3)	1 (1.3)	1 (1.3)
Musculoskeletal and Connective Tissue Disorders						
Back Pain	2 (2.6)	1 (1.3)	4 (5.4)	2 (2.6)	2 (2.6)	1 (1.3)
Arthralgia	3 (3.9)	0 (0.0)	1 (1.4)	4 (5.3)	1 (1.3)	1 (1.3)
Pain in Extremity	2 (2.6)	1 (1.3)	1 (1.4)	1 (1.3)	1 (1.3)	0 (0.0)
Investigations						
Smear Cervix Abnormal	2 (2.6)	0 (0.0)	1 (1.4)	1 (1.3)	0 (0.0)	2 (2.6)
GGT Increased	2 (2.6)	0 (0.0)	2 (2.7)	1 (1.3)	0 (0.0)	0 (0.0)
General Disorders and Administrative Site Conditions						
Fatigue	0 (0.0)	0 (0.0)	2 (2.7)	2 (2.6)	1 (1.3)	1 (1.3)
Respiratory, Thoracic and Mediastinal Disorders						
Cough	0 (0.0)	0 (0.0)	2 (2.7)	1 (1.3)	1 (1.3)	1 (1.3)
Psychiatric Disorders						
Insomnia	0 (0.0)	1 (1.3)	1 (1.4)	3 (3.9)	1 (1.3)	2 (2.6)
Depression	0 (0.0)	2 (2.7)	0 (0.0)	1 (1.3)	1 (1.3)	1 (1.3)
Vascular Disorders						
Hypertension	2 (2.6)	2 (2.7)	1 (1.4)	1 (1.3)	0 (0.0)	0 (0.0)
Immune System Disorders						
Seasonal Allergy	1 (1.3)	0 (0.0)	1 (1.4)	2 (2.6)	1 (1.3)	0 (0.0)

Source: Table 14, Primary Medical Review, signed July 27, 2007.

Division Director's Comment

- *As would be expected, breast pain was reported in ≥ 5% of subjects in each of the estrogen treatment groups.*
- *The types of adverse events reported and the reported frequencies of these events are comparable to those seen in other short-term studies of estradiol for the treatment of VMS. The adverse event profile does not raise any concerns about the safety of Evamist, beyond those for estrogen products in general.*

6.4 Overall Assessment of Safety

The systemic safety profile of transdermal estrogen products is well established. Serum concentrations of estradiol in subjects treated with Evamist were within the range of those produced by previously approved transdermal estrogen products. Therefore, no additional safety issues, other than those that are based on the well established safety profile and risks associated with the use of systemic estrogen products, are expected for women who may use Evamist for treatment of VMS.

Local tolerance to Evamist in the clinical trials was acceptable.

7. OTHER DISCIPLINES

The findings of each of the non-medical review disciplines are well-summarized in the review of the Clinical Team Leader.

There are no unresolved toxicology, clinical pharmacology, or CMC (chemistry, manufacturing, or control) issues. The manufacturing facility has been inspected and has received an "Acceptable" recommendation from the Office of Compliance. The proposed trade name "Evamist" is acceptable to both the Division of Medication Errors and Technical Support (DMETS) and the Division of Drug Marketing, Advertising, and Communication (DDMAC).

8. LABELING

Acceptable labeling was submitted by the Applicant on July 26, 2007.

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

/s/

Scott Monroe
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MEDICAL OFFICER