CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-014

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

1.3 Administrative Documents

1.3.1 Patent Information

Information for the following patents is provided in Form FDA 3542a (attached):

Drug Product
Patent 6,299,900
Patent 6,818,226
Patent 6,978,945
Patent 6,923,983

Method of Use
Patent 6,299,900
Patent 6,818,226
Patent 6,923,983

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
22-014

NAME OF APPLICANT / NDA HOLDER
VIVUS, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
EVAMIST

ACTIVE INGREDIENT(S)	STRENGTH(S)
Estradiol	1.53 mg per spray

DOSAGE FORM
Metered dose transdermal spray

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,299,900- see attached sheet for additional patents	10/9/2001	2/19/2017

d. Name of Patent Owner	Address *(of Patent Owner)*	
Acrux DDS Pty Ltd	103-113 Stanley Street	
	City/State West Melbourne, VIC 3003	
	ZIP Code AUSTRALIA	FAX Number *(if available)* 61 3 8379 0101
	Telephone Number 61 3 8379 0100	E-Mail Address *(if available)* Unknown

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ Ivor Elrifi	Mintz Levin, 666 Third Avenue	
	City/State New York, New York	
	ZIP Code 10017	FAX Number *(if available)* 212 983 3115
	Telephone Number 212 692 6800	E-Mail Address *(if available)* irelrifi@mintz.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	☐ Yes	☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* #6,299,900, claims 8-12 - see attached sheet for additional patents	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

EvaMist (estradiol transdermal spray) is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause

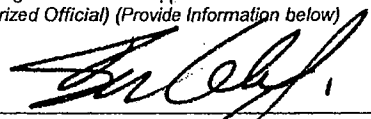
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	9/19/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Ivor Elrifi, Mintz Levin	
Address 666 Third Avenue	City/State New York, New York
ZIP Code 10017	Telephone Number 212 692 6800
FAX Number *(if available)* 212 983 3115	E-Mail Address *(if available)* irelrifi@mintz.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

NDA Number 22-014
Name of Applicant: VIVUS, Inc.

ADDENDUM TO SECTION 1:

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,818,226	11/16/2004	2/19/2017

d. Name of Patent Owner	Address of Patent Owner
ACRUX DDS Pty, Ltd.	103-113 Stanley Street West Melbourne, VIC 3003 AUSTRALIA Fax Number: 61 3 9905 4007 Telephone Number: 61 3 9902 6000

e. Name of agent	Address of agent
Ivor Elrifi	MINTZ LEVIN 666 Third Ave. New York, New York 10017 212 692 6800 irelrif@mintz.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? **NO**

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a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,978,945	12/27/2005	11/30/2021

d. Name of Patent Owner	Address of Patent Owner
ACRUX DDS Pty, Ltd.	103-113 Stanley Street West Melbourne, VIC 3003 AUSTRALIA Fax Number: 61 3 9905 4007 Telephone Number: 61 3 9902 6000

e. Name of agent	Address of agent
Ivor Elrifi	MINTZ LEVIN 666 Third Ave. New York, New York 10017 212 692 6800 irelrif@mintz.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? **NO**

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a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,923,983	8/2/2005	2/19/2017

d. Name of Patent Owner	Address of Patent Owner
ACRUX DDS Pty, Ltd.	103-113 Stanley Street West Melbourne, VIC 3003 AUSTRALIA Fax Number: 61 3 9905 4007 Telephone Number: 61 3 9902 6000

e. Name of agent	Address of agent
Ivor Elrifi	MINTZ LEVIN 666 Third Ave. New York, New York 10017 212 692 6800 irelrif@mintz.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? **NO**

ADDENDUM TO SECTION 4:

4.2	**Patent Claim Number**	**Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA?**
	#6,818,226, Claims 15-17, 19, 21	Yes
4.2a	**If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.**	**Use: *(Submit indication or method of use information as identified specifically in the approved labeling)*** EvaMist (estradiol transdermal spray) is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause.

4.2	**Patent Claim Number**	**Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA?**
	#6,923,983 Claims 11, 15, 16, 17-20	Yes
4.2a	**If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.**	**Use: *(Submit indication or method of use information as identified specifically in the approved labeling)*** EvaMist (estradiol transdermal spray) is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause.

EXCLUSIVITY SUMMARY

NDA # 22-014 SUPPL # HFD # 580

Trade Name Evamist

Generic Name estradiol transdermal spray

Applicant Name Vivus

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

None specified

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-538 Vivelle-Dot

NDA# 21-258 Climara Pro

NDA# 20-847 Esclim

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

EST-01

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

EST-01

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 62,606	YES ☒	! NO ☐
		! Explain:
Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Kassandra Sherrod, R.Ph.
Title: Project Management
Date: 6/26/07

Name of Office/Division Director signing form: DRUP/Scott Monroe, M.D.
Title: Acting Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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
7/27/2007 04:23:13 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-014 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: September 29, 2006 PDUFA Goal Date: July 29, 2007

HFD 580 Trade and generic names/dosage form: Evamist™ (estradiol transdermal spray)

Applicant: Vivus, Inc. Therapeutic Class: HRT

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

xYes. Please proceed to the next question.

❑ No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Treatment of moderate to severe vasomotor symptoms associated with menopause

s this an orphan indication?

❑ Yes. PREA does not apply. Skip to signature block.

xNo. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

xYes: Please proceed to Section A.

❑ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

❑ Products in this class for this indication have been studied/labeled for pediatric population

xDisease/condition does not exist in children

❑ Too few children with disease to study

❑ There are safety concerns

❑ Other: _____

f studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

tion B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

f there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ❑ **Yes. PREA does not apply. Skip to signature block.**
- ❑ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Kassandra C. Sherrod
6/28/2007 03:22:54 PM

1.3 Administrative Documents

1.3.8 Pediatric Waiver

A request for a Pediatric Waiver was submitted in IND 62, 602/S-0039 on June 23, 2006. In addition, the exclusion from pediatric study requirements for new drugs was discussed at the pre-NDA meeting on June 26, 2006. Copies of the relevant correspondence are attached.

VIVUS

June 23, 2006

Daniel Shames, MD, Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

RE: IND 62,602 / S-0039
Estradiol Transdermal Spray for the Treatment of Vasomotor Symptoms in Postmenopausal Women
Request for Pediatric Waiver

Dear Dr. Shames:

Reference is made to IND 62,602 for estradiol transdermal spray. VIVUS, Inc. expects to file NDA 22-014 for the treatment of moderate to severe vasomotor symptoms associated with surgical or natural menopause under the trade name EvaMist™ in the second half of 2006.

By way of this letter, VIVUS is requesting a full pediatric waiver for this upcoming NDA for EvaMist. As support for this full waiver request, VIVUS references the Guidance for Industry: How to Comply with the Pediatric Research Equity Act, Attachment A, item 2(a) which lists menopause symptoms as one of the qualifying criteria which does not require further statutory reasons for waiver of pediatric studies. Attached to this letter, please find a certification that this product qualifies for this full waiver **(Attachment 1)**.

Thank you for your continued support of the development of EvaMist. Please do not hesitate to contact Donna Kato at 408-857-4453 or via email at donna@regprofessional.com if you have questions regarding this pediatric waiver request.

Sincerely,

Peter Tam
Senior VP, Product and Corporate Development

PT/sgh
Enclosures

VIVUS, Inc. 1172 Castro Street, Mountain View, CA 94040 Tel 650-934-5200 Fax 650-934-5389 www.vivus.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: January 31, 2006
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
VIVUS, Inc.

2. DATE OF SUBMISSION
6/23/06

3. ADDRESS *(Number, Street, City, State and Zip Code)*
1172 Castro Street
Mountain View, CA 94040

4. TELEPHONE NUMBER *(Include Area Code)*
(650) 934-5200

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Estradiol MDTS

6. IND NUMBER *(If previously assigned)*
62, 602

7. INDICATION(S) *(Covered by this submission)*
For the treatment of moderate to severe vasomotor symptoms and vaginal atrophy associated with menopause

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☐ PHASE 2 ☑ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

DMF No. — DMF No. — DMF No. — b(4)

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
0 0 3 9

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☑ OTHER Pediatric Waiver Request *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ **TREATMENT IND 21 CFR 312.35(b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.35(a)** ☐ **CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)**

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

FORM FDA 1571 (1/03) PREVIOUS EDITION IS OBSOLETE. PAGE 1 OF 2

PSC Media Arts (301) 443-1090 EF

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- [x] 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- [ ] 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- [ ] 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- [ ] 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- [ ] 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- [ ] 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - [ ] a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - [ ] b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [ ] c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [ ] d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- [ ] 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - [ ] Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- [ ] 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- [ ] 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- [x] 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? [ ] YES [x] NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? [ ] YES [ ] NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Leland Wilson, Project Leader

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Wesley Day, Ph.D., VP Clinical Development

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Peter Tam Sr. VP, Product & Corporate Development		
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
1172 Castro Street Mountain View, CA 94040	(650) 934-5200	6/23/06

(**WARNING**: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

FORM FDA 1571 (1/03)

PAGE 2 OF 2

Attachment 1

PEDIATRIC WAIVER REQUEST

Product Name:	EvaMist™ (estradiol transdermal spray)
NDA #:	22-014
Applicant:	VIVUS, Inc.
Indications:	Estradiol transdermal spray for the treatment of vasomotor symptoms in postmenopausal women

This waiver request applies to all pediatric age groups.

With regard to all pediatric age groups, this waiver is sought based on established criteria. Since menopause is listed as an adult-related condition that does not affect pediatric patients, we hereby request that the FDA grant a full waiver in accordance with 505B(a)(4)(A)(i) of the Act, of the pediatric assessment requirements.

I, the undersigned, do hereby certify that the proposed product meets the criteria for a full waiver.

Sincerely,

Peter Tam
Senior VP, Product and Corporate Development

VIVUS

DEBARMENT CERTIFICATION

Regarding Original NDA 22-014, EvaMist™ (estradiol transdermal spray).

I, the undersigned, do hereby certify that VIVUS, Inc. did not and will not use in any capacity the services of any person debarred under section 306 of the Food, Drug, and Cosmetic Act in connection with this application.

Leland F. Wilson
President & CEO

9/23/04
Date

VIVUS, Inc. 1172 Castro Street, Mountain View, CA 94040 Tel 650-934-5200 Fax 650-934-5389 www.vivus.com

MEMORANDUM OF TELECON

DATE: June 19, 2007

APPLICATION NUMBER: NDA 22-014

BETWEEN:

Name: Jacqueline A. Dombroski, Ph.D.
Phone: 650-934-5288
Representing: VIVUS, Inc.

AND

Name: Karl Stiller, Office of New Drug Quality Assessment Project Manager
Division of PreMarketing Assessment III and Manufacturing Science

SUBJECT: Request by Firm for teleconference to clarify question in IR Letter.

On June 19, 2007, Dr. Dombroski called with a request for a teleconference with the chemistry reviewer to clarify a question sent to the Firm by FDA in an Information Request letter dated May 21, 2007. Dr. Dombroski was asked to send an email with the Firm's specific concerns so that the chemistry reviewer may have a better understanding of the Firm's need for clarification. The information emailed to FDA was reviewed, and a response (below) was communicated to the Firm via telephone and email. Dr. Dombroski verbally stated that there was no longer a need for a teleconference in light of the response from the chemistry reviewer.

****

From: Stiller, Karl
Sent: Tuesday, June 19, 2007 11:25 AM
To: Jacqueline Dombroski
Cc: Athey, Linda
Subject: RE: NDA 22-014; EvaMist: Request for Telecon to discuss Point 2 with ONDQA
Sensitivity: Confidential

Your response (attached below) to point 2 of FDA's Information Request letter has been reviewed by the Pharmaceutical Assessment Lead and Chemistry Reviewer to whom this application is assigned. It has been determined to be adequate, and no teleconference is deemed necessary. Please officially submit this response, as well as your responses to points 1 and 3 through 8 to the NDA.

LT Karl Stiller, RPh
Regulatory Health Project Manager
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research
301-796-1993

From: Jacqueline Dombroski [mailto:dombroski@vivus.com]
Sent: Monday, June 18, 2007 9:23 PM
To: Stiller, Karl
Cc: Athey, Linda; Sherrod, Kassandra C; Peter Tam; Ted Broman
Subject: NDA 22-014; EvaMist: Request for Telecon to discuss Point 2 with ONDQA
Importance: High
Sensitivity: Confidential

Dear Mr. Stiller:
With reference to our telephone conversation today, 18 June 2007, I am sending you the letter requesting the telconference with ONDQA reviewers to discuss Point 2 of the Information Request Letter dated 21 May 2007. The enclosed letter includes VIVUS participants and the topics for discussion.

VIVUS participants can be available on Tuesday 19 June, any time after 12 noon EST/9:00 am PST. We suggest that we use VIVUS telephone conference service for which the call in numbers are as follows:

Dial-in number: 1-866-394-4146
Participant Code: 16364445

If you have any questions please do not hesitate to call me at 650 934 5288 or contact me by email at dombroski@vivus.com.

Kind regards, <<NDA_22014_Request for Tcon_2007_06_18.pdf>>

Jacqui Dombroski

Jacqueline A. Dombroski, Ph.D.
Senior Director Regulatory Affairs
VIVUS, Inc.
1172 Castro Street
Mountain View
CA 94040
Direct: 650 934 5288
Fax: 650 934 5212
Mobile: 650 7961076
dombroski@vivus.com

VIVUS

18 June 2007

Moo-Jhong Rhee, Ph.D., Chief, Branch III,
Pre-Marketing Assessment Division II,
Office of New Drug Quality Assessment
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: Original New Drug Application NDA 22-014
EvaMist™ (estradiol transdermal spray)
Request for Teleconference to Discuss Point 2 of the Information Request Letter and Topics for Discussion

For the attention of: Karl Stiller, Regulatory Health Project Manager for Quality

Dear Mr. Stiller:

With reference to our telephone conversation today, 18 June 2007, as you requested, I am forwarding a written Request for a Telephone Conference to Discuss Point 2 of the CMC Information Request Letter that was sent to VIVUS on 21 May 2007 together with the topics that the company wishes to discuss. VIVUS is requesting this telephone conference to ensure that the company understands the reviewers concerns regarding the "overfill" of the EvaMist product vial and can respond appropriately to Point 2.

The Original New Drug Application (NDA) was submitted under Section 505(b) of the Federal Food, Drug and Cosmetic Act for EvaMist (estradiol transdermal spray), VIVUS, Inc.(VIVUS) on 6 September 2006. The Information Request Letter from Moo-Jhong Ree, Ph.D., dated 21 May 2007, contained comments and information requests from the Office of New Drug Quality Assessment (ONDQA) on the chemistry, manufacturing and controls (CMC) section of the NDA.

VIVUS provided responses to Point 1 and Points 3 through 8 of the Information Request Letter in NDA Amendment Number 12, submitted 18 June 2007. In an electronic message sent to Ms. Linda Athey on 15 June 2007, VIVUS requested a telephone conference to discuss Point 2 of the Information Request Letter with representatives of ONDQA at the earliest, mutually convenient date and time.

Following our telephone conversation on 18 June 2007, VIVUS is now requesting a telephone conference on **Tuesday 19 June 2007 after 12:00 noon EST/9:00 am**

VIVUS, Inc. 1172 Castro Street, Mountain View, CA 94040 Tel 650-934-5200 Fax 650-934-5369 www.vivus.com

PST. If that is not convenient, VIVUS welcomes other suggestions for dates and times for the telephone conference in order to promptly discuss Point 2 and complete the responses.

VIVUS' participants will be: Ted Broman, Sr. Director of Chemistry, Manufacturing and Control; Peter Tam, M.B.A., Sr. V.P. Product and Corporate Development and myself, Jacqueline Dombroski, Ph.D., Sr Director Regulatory Affairs.

Please use the following call-in numbers for the telephone conference:

Telephone Dial-in Number : 1-866- 394-4146
Participant code: 16364445

As requested, background information and specific topics that VIVUS is seeking to discuss follow:

1. BACKGROUND

FDA Point 2 from the Information Request Letter:

To help determine if the proposed overfill of the container is justified and prevent incorrect dose if the product is misused after labeled number of sprays, please provide profile of the sprays (e.g. content uniformity, spray pattern, and actuation force) near container exhaustion (e.g. the container is close to empty).

Please refer to the following sections in Modules 2 and 3 of the NDA:

NDA 22-014, Section 2.3.P.5.1 "*Justification of Specifications: Minimum Fill*"
Module 2, Volume 1, Page 42 of 183 states the following:

"Minimum Fill
The proposed specification conforms to USP <755> criteria. Each container contains 8.1 mL and is designed to deliver 56 sprays of 90 µL each after priming. Dimensional tolerances of the vial and pump were used to determine the fill volume required to assure that 56 sprays could be dispensed. Three priming pump actuations are used prior to the first spray. A 30% tilt was assumed to assure that the patient would receive 56 sprays even when tilting the applicator. These calculations assume the pump is delivering at the individual pump specification limit of + — of the target volume of 90 µL."

b(4)

Further information is provided in NDA 22-014 Module 3, Volume 3, 3.2.P.5.6.11, page 195 and 196, entitled "*Minimum Fill*", as follows:

"3.2.P.5.6.11 Minimum Fill

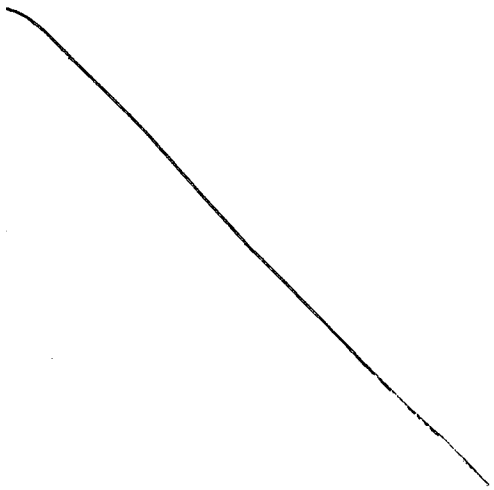
The proposed specification for minimum fill is as follows:

Acceptance Criteria	Assay	Method
Mean not less than labeled volume and none less than 90% of labeled volume on 10 units tested.	Weight	USP <755>

The proposed specification conforms to USP <755> criteria. Each container contains 8.1 mL and is designed to deliver 56 sprays of 90 µL each after priming. Table 3.2.P.5-5 lists the dimensional tolerances of the vial and pump used to determine the fill volume required to assure that 56 sprays could be dispensed. Three priming pump actuations are used prior to the first spray. A 30% tilt was assumed to assure that the patient would receive 56 sprays even when tilting the applicator. These calculations assume the pump is delivering at the individual pump specification limit of [redacted] of the target volume of 90 µL.

b(4)

Table 3.2.P.5-5 Dimensional Tolerances of the Vial and Pump



b(4)

2. VIVUS' DISCUSSION POINTS

2.1. The justification for the Minimum Fill, that includes the "overfill", was presented in the NDA in the sections that have been repeated in the "BACKGROUND" section of this letter. The calculations, based on the actual data given in Table 3.2.P.5-5 *Dimensional Tolerances of the Vial and Pump,* lead to the choice of the fill volume. Due to the dimensional tolerances, the position of the stiff, straight, dip tube and the pump performance, the overfill must be adequate in order to ensure the actual delivery of the required minimum of 56 sprays to the patient. VIVUS would appreciate the opportunity to explain the calculations to the ONDQA reviewers.

Would the ONDQA reviewers provide more background on their specific concerns because the company is uncertain that the experimental data requested will provide an adequate response to the concern about "overfill" raised in Point 2?

2.2 The pump is expected to perform according to the manufacturer's specifications, therefore, it will permit additional sprays beyond the 56 sprays on the label. However, VIVUS also calculated that if a patient were to ignore the labeled indications and spray to exhaustion, between approximately 2 and 20 extra sprays would be obtained depending upon the orientation of the product used by the patient.

2.3 VIVUS is concerned that it is not possible to perform an experiment that generates data to emulate the "worst case" scenario on which the calculations for Minimium Fill Volume were based.

In conclusion, VIVUS rationale and calculation for the Minimum Fill Volume that VIVUS submitted in the NDA took the vial and pump vendor's specification limits and VIVUS' experience during product development into account to derive the "worst case" volume required to assure all product units would provide the labeled number of sprays to a patient. VIVUS is not certain that the experimental data requested by the ONDQA reviewers will address their concern about "overfill".

This letter is being submitted as correspondence and only by electronic mail. Please do not hesitate to contact me by telephone at 650 934 5288 or by electronic mail at dombroski@vivus.com if you require any additional information or have any further questions.

J. A. Dombroski

Sincerely,
Jacqueline Dombroski, Ph.D.
Sr. Director, Regulatory Affairs

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

/s/

Karl Stiller
6/20/2007 09:01:56 AM
PROJECT MANAGER FOR QUALITY

Donna Christner
6/21/2007 09:06:40 AM
CHEMIST

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-014 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Evamist
Established Name: estradiol
Strengths: 1.53 mg

Applicant: Vivus
Agent for Applicant (if applicable):

Date of Application: September 28, 2006
Date of Receipt: September 29, 2006
Date clock started after UN:
Date of Filing Meeting: November 15, 2006
Filing Date: November 28, 2006
Action Goal Date (optional): July 29, 2007 User Fee Goal Date:

Indication requested: Treatment of moderate to severe vasomotor symptoms associated with menopause

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 2
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☐ NO ☒
  If no, explain:

- Was form 356h included with an authorized signature? YES ☐ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☐ NO ☒
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☒

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☐ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☐
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

   Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, x Years NO ☐
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 62,602

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) April 22, 2003 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) May 31, 2006 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☒ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☐ NO ☒
  If no, did applicant submit a complete environmental assessment? YES ☒ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☒ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☒

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 15, 2006

NDA #: 22-014

DRUG NAMES: Evamist

APPLICANT: Vivus

BACKGROUND: This molecular entity is already approved. This is a new dosage form.
(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES:

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	Price
Secondary Medical:	Slauhter
Statistical:	Castillo
Pharmacology:	Mckinney
Statistical Pharmacology:	
Chemistry:	Christner
Environmental Assessment (if needed):	
Biopharmaceutical:	Kim
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
OPS:	
Regulatory Project Management:	Sherrod
Other Consults:	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☐ NO ☒
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A	☒	FILE	☐	REFUSE TO FILE	☐
STATISTICS	N/A	☐	FILE	☒	REFUSE TO FILE	☐
BIOPHARMACEUTICS			FILE	☒	REFUSE TO FILE	☐

- Biopharm. study site audits(s) needed? YES ☐ NO ☐

PHARMACOLOGY/TOX	N/A	☐	FILE	☒	REFUSE TO FILE	☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY			FILE	☒	REFUSE TO FILE	☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☐ NO ☒

  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Kassansdra Sherrod, R.Ph.

Regulatory Project Manager

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

/s/

Kassandra C. Sherrod
6/18/2007 09:35:00 AM
CSO

ACTION PACKAGE CHECKLIST

Application Information			
...A # NDA # 22-014	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type	
Proprietary Name: estradiol transdermal Established Name: Evamist ™ Dosage Form: Spray		Applicant: Vivus, Inc.	
RPM: Sherrod		Division: Reproductive and Urologic Products	Phone # 301-796-0997

NDAs: NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	July 29, 2007
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 2

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☐ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action

❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☒ DMETS 7/2/07 ☒ DSRCS 2/12/07 ☒ DDMAC 6/12/07 ☐ SEALD ☐ Other reviews ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	11/20/06
NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	n/a
❖ Pediatric Page (all actions)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☒ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	x
❖ Internal memoranda, telecons, email, etc.	x
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 6/28/06
• EOP2 meeting *(indicate date)*	☐ No mtg 4/22/03
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	7/18/07
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☐ None 7/27/07
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☒ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See CMC review p. 59
• ☐ Review & FONSI *(indicate date of review)*	N/A
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☒ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 11/8/06 ☒ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☒ Completed Pg 31 of CMC review ☐ Requested ☐ Not yet requested ☐ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	5/21/07
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	☒ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☒ None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	
Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
• Clinical Studies	
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☐ None 7/2/07
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 7/10/07

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
VIVUS INC Peter Tam 1172 CASTRO ST MOUNTAIN VIEW CA 94040 US	22-014
2. TELEPHONE NUMBER 650-934-5309	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? [X] YES [ ] NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: [X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION [ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
3. PRODUCT NAME EvaMist (Estradiol)	6. USER FEE I.D. NUMBER PD3006727

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act	[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	SVP, Product & Corp. Dev.	09/08/06

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$767,400.00

Form FDA 3397 (12/03)

IBE_PRMT_CLOSE_G) (Print Cover sheet)