# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPROVAL PACKAGE FOR:

## APPLICATION NUMBER

**NDA 21-632**
**NDA 21-948**

# Administrative/Correspondence Reviews

Vicuron
Pharmaceuticals

NDA Item 14: Patent Certification

NDA 21-948

Patent Certification - 21 U.S.C. 355 (b) (2) or (j) (2) (A)

Vicuron Pharmaceuticals Inc. hereby certifies that the provisions of 21 U.S.C. 355 (b) (2) or (j) (2) (A) do not apply to this application.

Signed: _____ Date: 6/28/05

Martin Stogniew, PhD
Executive Vice President, Scientific Affairs
Vicuron Pharmaceuticals Inc.

Vicuron
Pharmaceuticals

# NDA Item 13: Patent Information

# NDA 21-632 EC Amendment

Information pertaining to patents 5,965,525 & 6,384,013 was submitted in Original NDA 21-632 on April 25, 2003.

New patent information, to add patent 6,743,777 B1 was provided on June 22, 2004, in an Amendment to NDA 21-632.

Provided with this submission is updated (expiration date) information on patent #6,743,777 B1.

Appears This Way
On Original

455 South Gulph Road
Suite 310
King of Prussia, PA 19406

610 491.2200
610 491.2298

www.vicuron.com

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: 7/31/06
*See OMB Statement on Page 3.*

NDA NUMBER
21-632

NAME OF APPLICANT / NDA HOLDER
Vicuron Pharmaceuticals 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)
—

| ACTIVE INGREDIENT(S) | STRENGTH(S) |
|---|---|
| Anidulafungin | 50 mg vials |

DOSAGE FORM
IV

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 submit 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 |
|---|---|---|
| 6,743,777 B1 | 06/01/2004 | 03/19/2012 |

d. Name of Patent Owner
Eli Lilly and Company

Address *(of Patent Owner)*
P.O. Box 6288

City/State
Indianapolis, Indiana - USA

| ZIP Code | FAX Number *(if available)* |
|---|---|
| 46206 | (317) 277-1917 |
| Telephone Number | E-Mail Address *(if available)* |
| (317) 277-6467 | janusz_james_m@lilly.com |

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)

☞ Morrison & Foerster, LLP

Address *(of agent or representative named in 1.e.)*
755 Page Mill Road

City/State
Palo Alto, California

| ZIP Code | FAX Number *(if available)* |
|---|---|
| 94304 | (650) 494-0792 |
| Telephone Number | E-Mail Address *(if available)* |
| (650) 813-5740 | KBolin@mofo.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


PSC Media Arts (301) 443-1090 EF

***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** Claim Number (*as listed in the patent*)<br>3,4,10,11,12,13 | 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 proposed labeling.)*<br>See attached sheet. | | |

## 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 |
|---|---|
| [signature] | 5/18/05 |

**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<br>Vicuron Pharmaceuticals Inc. | |
| Address<br>455 South Gulph Road, Suite 305 | City/State<br>King of Prussia, Pennsylvania - USA |
| ZIP Code<br>19406 | Telephone Number<br>(610) 491-2203 |
| FAX Number *(if available)*<br>(610) 491-2298 | E-Mail Address *(if available)*<br>mstogniew@vicuron.com |

Attachment pertaining to Section 4.2 – Method of Use

Do the patent claims (2, 5, 8,9,14 & 15) claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? No.

Uses for which the answer to 4.2 is Yes: 3, 4, 10, 11, 12 & 13

3. Microbiology-Mechanism of Action and Clinical Studies-Esophageal Candidiasis; A method of inhibiting fungal activity (anidulafungin inhibits the synthesis of 1,3-ß-D glucan, an essential component of the fungal cell wall) comprising a formulation of claim 1 with a fungus.

4. Microbiology-Activity in vivo and Clinical Studies-Esophageal Candidiasis; A method of inhibiting the growth of organisms responsible for opportunistic infections in immunosuppressed individuals comprising administering a formulation of claim 1 to said individual.

10. Microbiology-Mechanism of Action and Clinical Studies-Esophageal Candidiasis; A method of inhibiting fungal activity comprising contacting a formulation of claim 6 with a fungus.

11. Microbiology-Mechanism of Action and Clinical Studies-Esophageal Candidiasis; The method of claim 10, wherein R is $-O(CH_2)_4CH_3$.

12. Microbiology-Activity in vivo and Clinical Studies-Esophageal Candidiasis; A method of inhibiting the growth of organisms responsible for opportunistic infections in immunosuppressed individuals comprising administering a formulation of claim 6 to said individual.

13. Microbiology-Activity in vivo and Clinical Studies-Esophageal Candidiasis; The method of claim 12, wherein R is $-O(CH_2)_4CH_3$.

Vicuron
Pharmaceuticals

NDA Item 14: Patent Certification

NDA 21-632

Patent Certification - 21 U.S.C. 355 (b) (2) or (j) (2) (A)

Vicuron Pharmaceuticals Inc. hereby certifies that the provisions of 21 U.S.C. 355 (b) (2) or (j) (2) (A) do not apply to this application.

Signed: Timothy J Henkel Date: 30 April 2003

Timothy J. Henkel, MD, PhD
Executive Vice President and Chief Medical Officer
Vicuron Pharmaceuticals Inc.

Time Sensitive Patent Information

pursuant to 21 C.F.R. 314.53

for

NDA #21-632

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The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: **TBD (To be Determined)**
- Active Ingredient(s): **Anidulafungin**
- Strength(s): **50 mg Vials**
- Dosage Form: **Intravenous**
- Approval Date: **Pending**

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# A. U.S Patent Information:

## U.S. Patent Number: 5,965, 525

**Expiration Date: October 12, 2016**

**Type of Patent--Indicate all that apply:**

1. Drug Substance(Active Ingredient) __X__ Y ___N
2. Drug Product(Composition/Formulation) __X__ Y ___N
3. Method of Use __X__ Y ___N

a. Method(s) of use for which approval is being sought that are covered by the patent: **treatment of esophageal candidiasis.**

**Name of Patent Owner: Eli Lilly & Co.**

**U.S. Agent (if patent owner or applicant does not reside or have place of business in the US): N/A**

## B. Statement required by 21CFR 314.53.

The undersigned declares that the above stated United States Patent Number **5,965, 525** covers the composition, formulation and/or method of use of **anidulafungin**. This product is:

- ___currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

OR

- __X__the subject of this application for which approval is being sought.)

Signed: Timothy J. Henkel
Date: 3 April 2003
Title (optional):
Telephone Number (optional):

Appears This Way
On Original

Time Sensitive Patent Information

pursuant to 21 C.F.R. 314.53

for

NDA #21-632

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: **TBD (To be Determined)**
- Active Ingredient(s): **Anidulafungin**
- Strength(s): **50 mg Vials**
- Dosage Form: **Intravenous**
- Approval Date: **Pending**

# A. U.S Patent Information:

## U.S. Patent Number: 6,384,013

**Expiration Date: March 19, 2012**

**Type of Patent--Indicate all that apply:**

4. Drug Substance(Active Ingredient) __X__ Y ___ N
5. Drug Product(Composition/Formulation) ___ Y __X__ N
6. Method of Use ___ Y __X__ N

**Name of Patent Owner: Eli Lilly & Co.**

**U.S. Agent (if patent owner or applicant does not reside or have place of business in the US): N/A**

# EXCLUSIVITY SUMMARY

NDA # 21-632 and 21-948 SUPPL # N/A HFD # 590

Trade Name Eraxis

Generic Name anidulafungin

Applicant Name Pfizer

Approval Date, If Known February 17, 2006

## 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.

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

N/A

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?

N/A

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#

NDA#

NDA#

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:

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"):

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 # | 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: Kristen Miller, Pharm.D.
Title: Regulatory Health Project Manager
Date: February 9, 2006

Name of Office/Division Director signing form: Renata Albrecht, M.D.
Title: Director, Division of Special Pathogen and Transplant Products

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

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

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/s/

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Renata Albrecht
2/10/2006 05:29:23 PM

# PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

**NDA/BLA # :** 21-948 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

**Stamp Date:** August 18, 2005 **PDUFA Goal Date:** February 17, 2006

**HFD** 590 **Trade and generic names/dosage form:** Eraxis (anidulafungin) for intravenous use

**Applicant:** Pfizer **Therapeutic Class:** Antifungal

**Indication(s) previously approved:** N/A

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

**Number of indications for this application(s):** 1

**Indication #1:** Candidemia and other forms of Invasive candidiasis

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

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

## ection 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:**

| | | | | | |
|---|---|---|---|---|---|
| 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:**

| | | | | |
|---|---|---|---|---|
| **Min** _____ | **kg**_____ | **mo.** 0 | **yr.**_____ | **Tanner Stage**_____ |
| **Max**_____ | **kg**_____ | **mo.**_____ | **yr.** 16 | **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**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**

**Other:**_____

**Date studies are due (mm/dd/yy):** February 17, 2011

*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:**

| | | | | |
|---|---|---|---|---|
| **Min** _____ | **kg**_____ | **mo.**_____ | **yr.**_____ | **Tanner Stage**_____ |
| **Max**_____ | **kg**_____ | **mo.**_____ | **yr.**_____ | **Tanner Stage**_____ |

**Comments:**

*If 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:**

**Kristen Miller, Pharm.D., Regulatory Health Project Manager**

*{See appended electronic signature page}*

_____

**Regulatory Project Manager**

**cc: NDA 21-632**
**HFD-960/ Grace Carmouze**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

**(revised 12-22-03)**

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

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/s/

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Kristen Miller
2/9/2006 05:05:31 PM

# PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-632 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: April 25, 2003 PDUFA Goal Date: May 25, 2004

HFD 590 Trade and generic names/dosage form: [illegible] (anidulafungin) for intravenous use

Applicant: Vicuron Therapeutic Class: Antifungal

Indication(s) previously approved: N/A

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: Esophageal candidiasis

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

X 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.

## ection 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
X 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:

| | | | | | |
|---|---|---|---|---|---|
| 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:**

**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.*

## tion D: Completed Studies

**Age/weight range of completed studies:**

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

**Comments:**

*If 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: Kristen Miller, Pharm.D., Regulatory Project Manager**

*{See appended electronic signature page}*

_____
**Regulatory Project Manager**

**cc: NDA 21-632**
**HFD-960/ Grace Carmouze**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

**(revised 12-22-03)**

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

/s/

Kristen Miller
5/4/04 12:15:50 PM

# Demographic Worksheet

**Application Information** *(Enter all identifying information for the submission pertaining to this summary)*

**NDA Numbers:** 21-632 and 21-948 **Submission Type:** N/A **Serial Number:** N/A

**Populations Included In Application** *(Please provide information for each category listed below from the primary safety database excluding PK studies)*

| Category | | Number Exposed To Study Drug | | Number Exposed To Study Drug | | Number Exposed To Study Drug |
|---|---|---|---|---|---|---|
| Gender | Males | 334 | All Females | 298 | Females >50 | |
| Age: | 0-≤1 Mo. | 0 | >1 Mo.- ≤2Year | 0 | >2-≤11 | 12 |
| | 12-17 | 13 | 18-64 | Unknown | ≥65 | Unknown |
| Race: | White | 279 | Black | 207 | Asian | 50 |
| | Other | 96 | | | | |

**Gender-Based Analyses** *(Please provide information for each category listed below.)*

| Category | Was Analysis Performed? | | If no is checked, indicate which applies or provide comment below | |
|---|---|---|---|---|
| Efficacy | x Yes | ☐ No | ☐ Inadequate #'s | ☐ Disease Absent |
| Safety | x Yes | ☐ No | ☐ Inadequate #'s | ☐ Disease Absent |

| Was gender-based analysis included in labeling? | |
|---|---|
| Yes | No |
| ☐ | ☐ |
| ☐ | ☐ |

Is a dosing modification based on gender recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒ Sponsor ☐ FDA

**Age-Based Analyses** *(Please provide information for each category listed below)*

| Category | Was Analysis Performed? | | If no is checked, indicate which applies or provide comment below | |
|---|---|---|---|---|
| Efficacy | ☒ Yes | ☐ No | ☐ Inadequate #'s | ☐ Disease Absent |
| Safety | ☒ Yes | ☐ No | ☐ Inadequate #'s | ☐ Disease Absent |

| Was age-based analysis included in labeling? | |
|---|---|
| Yes | No |
| ☐ | ☐ |
| ☐ | ☐ |

Is a dosing modification based on age recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒ Sponsor ☐ FDA

**Race-Based Analyses** *(Please provide information for each category listed below)*

| Category | Was Analysis Performed? | | If no is checked, indicate which applies or provide comment below | |
|---|---|---|---|---|
| Efficacy | ☒ Yes | ☐ No | ☐ Inadequate #'s | ☐ Disease Absent |
| Safety | ☒ Yes | ☐ No | ☐ Inadequate #'s | ☐ Disease Absent |

| Was race-based analysis included in labeling? | |
|---|---|
| Yes | No |
| ☐ | ☐ |
| ☐ | ☐ |

Is a dosing modification based on race recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒ Sponsor ☐ FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

**Comment:**

The following comments are for the original submission of NDA 21-632.

1. Efficacy anaylses for demography was only done at end of therapy, and not at follow-up (another clinically relevant time point).
2. Only 17 patients of Hispanic ethnicity are in the Phase 2/3 database
3. In the ISS, the sponsor acknowledges insufficient independence of the variables age, geographic location, and ethnicity to draw conclusions regarding safety.

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

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/s/

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Kristen Miller
2/16/2006 08:45:13 AM

Vicuron
Pharmaceuticals

NDA Item 16: Debarment Certification

NDA 21-948

Debarment Certification (Federal Food, Drug, and Cosmetic Act, section 306(k)(1)

Vicuron Pharmaceuticals Inc. 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.

Signed: _____ Date: 6/27/05

David S. Krause, MD
Executive Vice President and Chief Medical Officer
Vicuron Pharmaceuticals Inc.

Vicuron
Pharmaceuticals

NDA Item 16: Debarment Certification

NDA 21-632

Debarment Certification (Federal Food, Drug, and Cosmetic Act, section 306(k)(1)

Vicuron Pharmaceuticals Inc. 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.

Signed: Timothy J. Henkel Date: 3 April 2003

Timothy J. Henkel, MD, PhD
Executive Vice President and Chief Medical Officer
Vicuron Pharmaceuticals Inc.

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

| Application Information | | |
|---|---|---|
| NDA: **21-632** | Efficacy Supplement Type SE- **N/A** | Supplement Number: **N/A** |
| Drug: **Eraxis (anidulafungin) for Injection** | Applicant: **Vicuron Pharmaceuticals Inc., a subsidiary of Pfizer** | |
| RPM: **Kristen Miller** | HFD-**590** | Phone # : **(301) 796-1600** |
| Application Type: **(X)** 505(b)(1) ( ) 505(b)(2) | Reference Listed Drug (NDA #, Drug name): **N/A** | |

| | | |
|---|---|---|
| ❖ Application Classifications: | | |
| • Review priority | | (**X** ) Standard ( ) Priority |
| • Chem class (NDAs only) | | **Class 1 (NME)** |
| • Other (e.g., orphan, OTC) | | **N/A** |
| ❖ User Fee Goal Dates | | **February 17, 2006** |
| ❖ Special programs (indicate all that apply) | | (**X**) None<br>Subpart H<br>( ) 21 CFR 314.510 (accelerated approval)<br>( ) 21 CFR 314.520 (restricted distribution)<br>( ) Fast Track<br>( ) Rolling Review |
| User Fee Information- | | |
| • User Fee | | (**X**) Paid - refunded |
| • User Fee waiver | **Letter granting User Fee waiver for Versicor, Inc., the original sponsor, included** | (**X**) Small business<br>( ) Public health<br>( ) Barrier-to-Innovation<br>( ) Other |
| • User Fee exception - | | () Orphan designation<br>( ) No-fee 505(b)(2) **N/A**<br>( ) Other |
| ❖ Application Integrity Policy (AIP) | | |
| • Applicant is on the AIP | | ( ) Yes (**X**) No |
| • This application is on the AIP | | ( ) Yes (**X**) No |
| • Exception for review (Center Director's memo) | | **N/A** |
| • OC clearance for approval | | **N/A** |
| ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent. | | (**X**) Verified |
| ❖ Patent- | | |
| • Information: Verify that patent information was submitted | | (**X**) Verified |
| • Patent certification [505(b)(2) applications]: Verify type of certifications submitted | | 21 CFR 314.50(i)(1)(*i*)(A)<br>( ) I ( ) II ( ) III ( ) IV **N/A**<br>21 CFR 314.50(i)(1)<br>( ) (ii) ( ) (iii) |
| • For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice). | | ( ) Verified **N/A** |

| | |
|---|---|
| Exclusivity (approvals only) | |
| • Exclusivity summary | **X- 2/10/06** |
| • Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!* | ( ) Yes, Application #_____<br>**(X)** No |
| ❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)* | **X - Filing Checklist (2/18/04 and 11/25/05)** |
| **General Information** | |
| ❖ Actions | |
| • Proposed action | **( X )** AP ( ) TA ( ) AE ( ) NA |
| • Previous actions (specify type and date for each action taken) | **AE on May 21, 2004 and November 25, 2005** |
| • Status of advertising (approvals only) | **( X )**Materials requested in AP letter<br>( ) Reviewed for Subpart H |
| ❖ Public communications | |
| • Press Office notified of action (approval only) | **(X )** Yes – in APPROVALS email<br>( ) Not applicable |
| • Indicate what types (if any) of information dissemination are anticipated | ( ) None<br>**( X )** Press Release<br>( ) Talk Paper<br>( ) Dear Health Care Professional Letter |
| Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable) | |
| • Division's proposed labeling (only if generated after latest applicant submission of labeling) | **N/A** |
| • Most recent applicant-proposed labeling | **X- "Eraxis" label combines labels for NDAs 21-632 and 21-948** |
| • Original applicant-proposed labeling | **X** |
| • Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)* | **DDMAC reviews: 1/9/04, 2/2/06, and 2/17/06**<br>**DMETS reviews: 12/2/03, 11/9/05 and 2/13/06**<br>**ODS review: 3/31/04** |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling) | **X- Mycamine (micafungin), Cancidas (caspofungin) and VFEND (voriconazole)** |
| ❖ Labels (immediate container & carton labels) | |
| • Division proposed (only if generated after latest applicant submission) | **N/A** |
| • Applicant proposed | **X** |
| • Reviews | **Under Label/Labeling Consults:**<br>**DMETS review: 12/2/03, 2/13/06** |
| ❖ Post-marketing commitments | |
| • Agency request for post-marketing commitments | **No PMCs requested** |
| • Documentation of discussions and/or agreements relating to post-marketing commitments | **N/A** |
| Outgoing correspondence (i.e., letters, E-mails, faxes) | **X- under Memos and Telecons** |
| ❖ Memoranda and Telecons | **Telecon- Extension of User Fee goal date: 1/14/04**<br>**Telecon- Review update: 3/16/04**<br>**Telecon- Review update: 4/19/04** |

| | |
|---|---|
| | **Telecon- Micro: 7/18/05** |
| ❖ Minutes of Meetings | |
| • EOP2 meeting (indicate date) | **X-1/31/02 (Minutes never finalized)** |
| • Pre-NDA meeting (indicate date) | **X- 7/29/02** |
| • Pre-Approval Safety Conference (indicate date; approvals only) | **X- 2/16/06** |
| • Other | **Reg. Briefing minutes (2/20/04)<br>Pre-resubmission mtg (3/21/05)<br>Pre-approval safety mtg (Pending)** |
| ❖ Advisory Committee Meeting | |
| • Date of Meeting | **N/A** |
| • 48-hour alert | **N/A** |
| ❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable) | **N/A** |
| **Summary Application Review** | |
| ❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)* | **X- Division Director and Deputy Office Director Review (5/21/04, 11/25/05 and 2/17/06)** |
| **Clinical Information** | |
| ❖ Clinical review(s) *(indicate date for each review)* | **X- Executive Summary (11/25/05)<br>X- Clinical Review (5/21/04, 11/25/05 and 2/17/06)<br>X- ODS Consults (Hepatotoxicity)** |
| Microbiology (efficacy) review(s) *(indicate date for each review)* | **X- (4/22/04, 11/21/05 and 2/16/06)** |
| ❖ Safety Update review(s) *(indicate date or location if incorporated in another review)* | **See Clinical Reviews (5/21/04, 11/25/05 and 2/17/06)** |
| ❖ Pediatric Page(separate page for each indication addressing status of all age groups) | **X- 5/4/04** |
| ❖ Demographic Worksheet *(NME approvals only)* | **X- 2/16/06** |
| ❖ Statistical review(s) *(indicate date for each review)* | **X- (3/31/04, 11/15/05 and 2/14/06)** |
| ❖ Biopharmaceutical review(s) *(indicate date for each review)* | **X- (5/14/04, 11/18/05, 2/14/06 and 2/16/06)** |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)* | **N/A** |
| ❖ Clinical Inspection Review Summary (DSI) | |
| • Clinical studies | **X- Consult requests<br>X- Clinical Inspections Summary<br>X –Canadian Inspection Review (2-10-06)<br>X- Final review of EIRs** |
| • Bioequivalence studies | **N/A** |
| **CMC Information** | |
| ❖ CMC review(s) *(indicate date for each review)* | **X- (4/29/04, 5/4/04 and 2/17/06)** |
| ❖ Environmental Assessment | |
| • Categorical Exclusion *(indicate review date)* | **X- See Chemistry Review (pg 16)** |
| • Review & FONSI *(indicate date of review)* | **N/A** |
| • Review & Environmental Impact Statement *(indicate date of each review)* | **N/A** |
| ❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)* | **Behind Chem Reviews (2/25/04)** |

| | |
|---|---|
| ❖ Facilities inspection (provide EER report) | Date completed: **5/4/04 (see review)**<br>**(X)** Acceptable<br>( ) Withhold recommendation |
| ❖ Methods validation **This is not required for approval.** | ( ) Completed<br>( ) Requested<br>( ) Not yet requested |
| **Nonclinical Pharm/Tox Information** | |
| ❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* | **X- (5/13/04, 11/22/05 and 2/16/06)** |
| ❖ Nonclinical inspection review summary | **N/A** |
| ❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | **N/A** |
| ❖ CAC/ECAC report | **N/A** |

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

| Application Information | | |
|---|---|---|
| NDA: **21-948** | Efficacy Supplement Type SE- **N/A** | Supplement Number: **N/A** |
| Drug: **Eraxis (anidulafungin) for Injection** | Applicant: **Pfizer Pharmaceuticals** | |
| RPM: **Kristen Miller** | HFD-590 | Phone # : **(301) 796-1600** |
| Application Type: **(X)** 505(b)(1) **( )** 505(b)(2) | Reference Listed Drug (NDA #, Drug name): **N/A** | |

| | |
|---|---|
| ❖ Application Classifications: | |
| • Review priority | ( ) Standard (X ) Priority |
| • Chem class (NDAs only) | Class 6 |
| • Other (e.g., orphan, OTC) | N/A |
| ❖ User Fee Goal Dates | **February 17, 2006** |
| ❖ Special programs (indicate all that apply) | **(X)** None<br>**Subpart H**<br>( ) 21 CFR 314.510 (accelerated approval)<br>( ) 21 CFR 314.520 (restricted distribution)<br>( ) Fast Track<br>( ) Rolling Review |
| ❖ User Fee Information- | |
| • User Fee | **(X)** Paid |
| User Fee waiver | ( ) Small business<br>( ) Public health<br>( ) Barrier-to-Innovation<br>( ) Other |
| • User Fee exception - | () Orphan designation<br>( ) No-fee 505(b)(2) **N/A**<br>( ) Other |
| ❖ Application Integrity Policy (AIP) | |
| • Applicant is on the AIP | ( ) Yes **(X)** No |
| • This application is on the AIP | ( ) Yes **(X)** No |
| • Exception for review (Center Director's memo) | **N/A** |
| • OC clearance for approval | **N/A** |
| ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent. | **(X)** Verified |
| ❖ Patent- | |
| • Information: Verify that patent information was submitted | **(X)** Verified- Referenced to 21-632 |
| • Patent certification [505(b)(2) applications]: Verify type of certifications submitted | 21 CFR 314.50(i)(1)(*i*)(A)<br>( ) I ( ) II ( ) III ( ) IV **N/A**<br>21 CFR 314.50(i)(1)<br>( ) (ii) ( ) (iii) |
| • For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice). | ( ) Verified **N/A** |

| | |
|---|---|
| Exclusivity (approvals only) | |
| • Exclusivity summary | **X- (Same as 21-632; 2/10/06)** |
| • Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!* | ( ) Yes, Application #_____<br>**(X)** No |
| ❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)* | **X - Filing Checklist (Same as 21-632)** |
| **General Information** | |
| ❖ Actions | |
| • Proposed action | ( X ) AP ( ) TA ( ) AE ( ) NA |
| • Previous actions (specify type and date for each action taken) | NDA 21-632 received AE on May 21, 2004 and November 25, 2005 |
| • Status of advertising (approvals only) | ( X )Materials requested in AP letter<br>( ) Reviewed for Subpart H |
| ❖ Public communications | |
| • Press Office notified of action (approval only) | **(X )** Yes – in APPROVALS email<br>( ) Not applicable |
| • Indicate what types (if any) of information dissemination are anticipated | ( ) None<br>**( X )** Press Release<br>( ) Talk Paper<br>( ) Dear Health Care Professional Letter |
| Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable) | |
| • Division's proposed labeling (only if generated after latest applicant submission of labeling) | **N/A** |
| • Most recent applicant-proposed labeling | **X- Eraxis label combines labels for NDAs 21-632 and 21-948** |
| • Original applicant-proposed labeling | **X** |
| • Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)* | **DDMAC reviews: Same as 21-632**<br>**DMETS reviews: Same as 21-632** CDS |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling) | **X- Mycamine (micafungin), Cancidas (caspofungin), and VFEND (voriconazole)** |
| ❖ Labels (immediate container & carton labels) | |
| • Division proposed (only if generated after latest applicant submission) | **N/A** |
| • Applicant proposed | **X** |
| • Reviews | **Under Label/Labeling Consults: DMETS review: Same as 21-632** |
| ❖ Post-marketing commitments | |
| • Agency request for post-marketing commitments | **No PMCs requested** |
| • Documentation of discussions and/or agreements relating to post-marketing commitments | **N/A** |
| ❖ Outgoing correspondence (i.e., letters, E-mails, faxes) | **X- Same as 21-632** |
| ❖ Memoranda and Telecons | **Telecons- Same as 21-632** |
| Minutes of Meetings | |
| • EOP2 meeting (indicate date) | **X- Same as 21-632** |
| • Pre-NDA meeting (indicate date) | **X- Same as 21-632** |

| | |
|---|---|
| • Pre-Approval Safety Conference (indicate date; approvals only) | **X- Same as 21-632** |
| • Other | **Same as 21-632** |
| ❖ Advisory Committee Meeting | |
| • Date of Meeting | **N/A** |
| • 48-hour alert | **N/A** |
| ❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable) | **N/A** |
| **Summary Application Review** | |
| ❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)* | **X- Same as 21-632** |
| **Clinical Information** | |
| ❖ Clinical review(s) *(indicate date for each review)* | X- Executive Summary (Same as 21-632)<br>X- Clinical Review (Same as 21-632)<br>**X- ODS Consults (Same as 21-632)** |
| ❖ Microbiology (efficacy) review(s) *(indicate date for each review)* | **X- Same as 21-632** |
| ❖ Safety Update review(s) *(indicate date or location if incorporated in another review)* | See Clinical Reviews (Same as 21-632) |
| ❖ Pediatric Page(separate page for each indication addressing status of all age groups) | X- 2/9/06 ✓ |
| ❖ Demographic Worksheet *(NME approvals only)* | X- Same as 21-632 |
| Statistical review(s) *(indicate date for each review)* | **X- Same as 21-632** |
| Biopharmaceutical review(s) *(indicate date for each review)* | X- Same as 21-632 |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)* | N/A |
| ❖ Clinical Inspection Review Summary (DSI) | |
| • Clinical studies | **X- Consult requests**<br>**X- Clinical Inspections Summary**<br>**X – Canadian inspection review**<br>**X- Final review of EIRs** |
| • Bioequivalence studies | **N/A** |
| **CMC Information** | |
| ❖ CMC review(s) *(indicate date for each review)* | **X- Same as 21-632** |
| ❖ Environmental Assessment | |
| • Categorical Exclusion *(indicate review date)* | **X- See Chemistry review** |
| • Review & FONSI *(indicate date of review)* | **N/A** |
| • Review & Environmental Impact Statement *(indicate date of each review)* | **N/A** |
| ❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)* | **Behind Chemistry Reviews (2/25/04)** |
| ❖ Facilities inspection (provide EER report) | Date completed: **5/4/04 (see review)**<br>**(X)** Acceptable<br>( ) Withhold recommendation |
| ❖ Methods validation **This is not required for approval.** | ( ) Completed<br>( ) Requested<br>( ) Not yet requested |
| **Nonclinical Pharm/Tox Information** | |
| ❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* | **X- Same as 21-632** |

| | | |
|---|---|---|
| | Nonclinical inspection review summary | **N/A** |
| ❖ | Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | **N/A** |
| ❖ | CAC/ECAC report | **N/A** |

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

| Application Information | | |
|---|---|---|
| NDA: **21-632** | Efficacy Supplement Type SE- **N/A** | Supplement Number: **N/A** |
| Drug: **Anidulafungin for Injection** | Applicant: **Vicuron Pharmaceuticals** | |
| RPM: **Kristen Miller** | HFD-**590** | Phone # : **(301) 827-2127** |
| Application Type: **(X)** 505(b)(1) ( ) 505(b)(2) | Reference Listed Drug (NDA #, Drug name): **N/A** | |

| | |
|---|---|
| ❖ Application Classifications: | |
| • Review priority | (X ) Standard ( ) Priority |
| • Chem class (NDAs only) | **Class 1 (NME)** |
| • Other (e.g., orphan, OTC) | **N/A** |
| ❖ User Fee Goal Dates | **May 25, 2004** |
| ❖ Special programs (indicate all that apply) | (X) None<br>Subpart H<br>( ) 21 CFR 314.510 (accelerated approval)<br>( ) 21 CFR 314.520 (restricted distribution)<br>( ) Fast Track<br>( ) Rolling Review |
| User Fee Information- | |
| • User Fee | (X) Paid - refunded |
| • User Fee waiver **Letter granting User Fee waiver included** | (X) Small business<br>( ) Public health<br>( ) Barrier-to-Innovation<br>( ) Other |
| • User Fee exception - | () Orphan designation<br>( ) No-fee 505(b)(2) **N/A**<br>( ) Other |
| ❖ Application Integrity Policy (AIP) | |
| • Applicant is on the AIP | ( ) Yes (X) No |
| • This application is on the AIP | ( ) Yes (X) No |
| • Exception for review (Center Director's memo) | **N/A** |
| • OC clearance for approval | **N/A** |
| ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent. | (X) Verified |
| ❖ Patent- | |
| • Information: Verify that patent information was submitted | (X) Verified |
| • Patent certification [505(b)(2) applications]: Verify type of certifications submitted | 21 CFR 314.50(i)(1)(*i*)(A)<br>( ) I ( ) II ( ) III ( ) IV **N/A**<br>21 CFR 314.50(i)(1)<br>( ) (ii) ( ) (iii) |
| • For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice). | ( ) Verified **N/A** |

| | |
|---|---|
| Exclusivity (approvals only) | |
| • Exclusivity summary | **N/A** |
| • Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!* | ( ) Yes, Application #_____<br>**(X)** No |
| ❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)* | **X - Filing Checklist** |
| **General Information** | |
| ❖ Actions | |
| • Proposed action | ( ) AP ( ) TA **(X)** AE ( ) NA |
| • Previous actions (specify type and date for each action taken) | **N/A** |
| • Status of advertising (approvals only) **N/A** | ( ) Materials requested in AP letter<br>( ) Reviewed for Subpart H |
| ❖ Public communications | |
| • Press Office notified of action (approval only) | ( ) Yes **(X)** Not applicable |
| • Indicate what types (if any) of information dissemination are anticipated | ( ) None<br>**(X)** Press Release<br>( ) Talk Paper<br>( ) Dear Health Care Professional Letter |
| ❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable) | |
| • Division's proposed labeling (only if generated after latest applicant submission of labeling) | **N/A** |
| • Most recent applicant-proposed labeling | **N/A** |
| • Original applicant-proposed labeling | **X** |
| • Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)* | **DDMAC reviews: 1/9/04**<br>**DMETS reviews: 12/2/03**<br>**ODS review: 3/31/04** |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling) | **N/A** |
| ❖ Labels (immediate container & carton labels) | |
| • Division proposed (only if generated after latest applicant submission) | **N/A** |
| • Applicant proposed | **X** |
| • Reviews | **Under Label/Labeling Consults:**<br>**DMETS review: 12/2/03** |
| ❖ Post-marketing commitments | |
| • Agency request for post-marketing commitments | **N/A** |
| • Documentation of discussions and/or agreements relating to post-marketing commitments | **N/A** |
| ❖ Outgoing correspondence (i.e., letters, E-mails, faxes) | **N/A** |
| ❖ Memoranda and Telecons | **Telecon- Extension of User Fee goal date: 1/14/04**<br>**Telecon- Review update: 3/16/04**<br>**Telecon- Review update: 4/19/04** |
| Minutes of Meetings | |
| • EOP2 meeting (indicate date) | **X-1/31/02 (Minutes never finalized)** |
| • Pre-NDA meeting (indicate date) | **X- 7/29/02** |
| • Pre-Approval Safety Conference (indicate date; approvals only) | **N/A** |

| | |
|---|---|
| • Other | **Reg. Briefing minutes (2/20/04)** |
| ❖ Advisory Committee Meeting | |
| • Date of Meeting | **N/A** |
| • 48-hour alert | **N/A** |
| ❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable) | **N/A** |
| **Summary Application Review** | |
| ❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)* | **X- Division Director and Deputy Office Director Review (5/21/04)** |
| **Clinical Information** | |
| ❖ Clinical review(s) *(indicate date for each review)* | **X- Executive Summary (5/21/04)**<br>**X- Clinical Review (5/21/04)**<br>**X- ODS Consults (Hepatotoxicity)** |
| ❖ Microbiology (efficacy) review(s) *(indicate date for each review)* | **X- (4/22/04)** |
| ❖ Safety Update review(s) *(indicate date or location if incorporated in another review)* | **See Clinical Review (5/21/04)** |
| ❖ Pediatric Page(separate page for each indication addressing status of all age groups) | **X- (5/4/04)** |
| ❖ Demographic Worksheet *(NME approvals only)* | **N/A** |
| ❖ Statistical review(s) *(indicate date for each review)* | **X- (3/31/04)** |
| ❖ Biopharmaceutical review(s) *(indicate date for each review)* | **X- (5/14/04)** |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)* | **N/A** |
| Clinical Inspection Review Summary (DSI) | |
| • Clinical studies | **X- Consult requests**<br>**X- Clinical Inspections Summary**<br>**X- Final review of EIRs** |
| • Bioequivalence studies | **N/A** |
| **CMC Information** | |
| ❖ CMC review(s) *(indicate date for each review)* | **X- (4/29/04 and 5/4/04)** |
| ❖ Environmental Assessment | |
| • Categorical Exclusion *(indicate review date)* | **X** |
| • Review & FONSI *(indicate date of review)* | **N/A** |
| • Review & Environmental Impact Statement *(indicate date of each review)* | **N/A** |
| ❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)* | **Behind Chem Reviews (2/25/04)** |
| ❖ Facilities inspection (provide EER report) | Date completed: **5/4/04 (see review)**<br>**(X)** Acceptable<br>( ) Withhold recommendation |
| ❖ Methods validation **This is not required for approval.** | ( ) Completed<br>( ) Requested<br>( ) Not yet requested |
| **Nonclinical Pharm/Tox Information** | |
| ❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* | **X- (5/13/04)** |
| Nonclinical inspection review summary | **N/A** |
| Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | **N/A** |
| ❖ CAC/ECAC report | **N/A** |

92 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT**
**OFFICE OF DRUG SAFETY**
**(DMETS; White Oak 22, Mail Stop 4447)**

| **DATE RECEIVED:** | **DESIRED COMPLETION DATE:** | **ODS CONSULT #:** |
|---|---|---|
| 12/15/2005 | 2/1/2006 | 05-0298-1 (name review) |
| **DATE OF DOCUMENT:** | **PDUFA DATE:** | and 05-0298-2 (labeling review) |
| 12/2/2005 | 2/18/2006 | |

**TO:** Renata Albrecht, MD
Director, Division of Special Pathogen and Transplant Products
HFD-590

**THROUGH:** Alina Mahmud, R.Ph., M.S., Team Leader
Denise Toyer, Pharm.D., Deputy Division Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD 420

**FROM:** Charlie Hoppes, R.Ph., M.P.H., Safety Evaluator
Division of Medication Errors and Technical Support, HFD 420

| **PRODUCT NAME:** | **SPONSOR:** Pfizer Inc. |
|---|---|
| **Eraxis®** (Anidulafungin for Injection), 50 mg<br><br>**NDA #'s:** 21-632 and NDA 21-948 | |

**RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name, Eraxis. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. [illegible]

   ] cs.

3. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-5038.

**Division of Medication Errors and Technical Support**
**Office of Drug Safety**
**(DMETS; White Oak 22, Mail Stop 4447)**
**Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** January 10, 2006

**NDA#'s:** 21-632 and 21-948

**NAME OF DRUG:** Eraxis® (Anidulafungin for Injection) 50 mg

**NDA HOLDER:** Pfizer Inc.

## I. INTRODUCTION:

This consult was written in response to a request from the Division of Special Pathogen and Transplant Products (HFD-590), for assessment of the proprietary name, "Eraxis" regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment. The [redacted] submitted a Proprietary Name Promotional Assessment in support of the proposed proprietary name.

This is the second name proposed for this drug product. In reviews dated November 4, 2003, (ODS 03-0248), March 18, 2004 (ODS 03-0248-1), and October 28, 2005 (ODS 05-0298), DMETS had no objection to the proposed proprietary name, [redacted] This application has recently transferred ownership to Pfizer Global Pharmaceuticals and despite acceptability of the [redacted] proprietary name, the new sponsor prefers the proprietary name, Eraxis.

PRODUCT INFORMATION

Eraxis (Anidulafungin for Injection) is indicated for treatment of esophageal candidiasis. Eraxis is supplied in a single-use 50 mg vial of sterile, lyophilized anidulafungin to be reconstituted with the diluent supplied with the product. The single-use diluent vial contains 15 mL of 20% (w/w) ethanol in Water for Injection. The usual adult dose proposed by the sponsor is a single 100 mg loading dose on the first day followed by 50 mg daily thereafter. The rate of infusion should not exceed 1.1 mg/minute Eraxis will be packaged in individual "units" (a 50 mg vial of anidulafungin for injection with a 15 mL vial of 20% w/w ethanol/water as a diluent) and trays of 10 units.

## II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Eraxis to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

### A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Eraxis. Potential concerns regarding drug marketing and promotion related to the proposed name(s) were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC

[1] MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

The review Division did not agree with DDMAC's objections and asked DMETS to review the name from a sound-alike/look-alike perspective.

2. The Expert Panel identified five proprietary names that were thought to have the potential for confusion with Eraxis. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

| Product Name | Dosage Form | Usual Dosage | Other |
|---|---|---|---|
| Eraxis | Anidulafungin for Injection, 50 mg | 100 mg loading dose followed by 50 mg daily thereafter by intravenous infusion | |
| Evoxac | Cevimiline Hydrochloride Capsules, 30 mg (base) | Take one capsule three times daily. | SA/LA |
| Eurax Cream<br>Eurax Lotion | Crotamiton Cream, 10%<br>Crotamiton Lotion, 10% | Apply to body, chin down followed by an additional application 24 hours later. | SA/LA |
| Plenaxis | Abaralix for Injection, 100 mg/vial | The recommended dose of abaralix is 100 mg intramuscularly to the buttock on days 1, 15, 29 (week 4), and every 4 weeks thereafter. | SA/LA |
| Errin | Norethindrone Tablets, 0.35 mg | Take one tablet daily to prevent conception. | LA |
| Uracid | Methionine Capsules, 200 mg | Take one capsule three to four times daily after meals. | SA/LA |
| *Frequently used, not all-inclusive.<br>**L/A (look-alike), S/A (sound-alike) | | | |

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Eraxis were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Eraxis with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 119 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Eraxis (page 5). These prescriptions were optically scanned and one

prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

| HANDWRITTEN PRESCRIPTION | VERBAL PRESCRIPTION |
|---|---|
| Outpatient RX:<br>Eraxis 50mg<br>1 vial<br>To be used in clinic as directed | Eraxis 50 mg<br>Dispense one vial.<br>To be used in clinic as directed. |
| Inpatient RX:<br>Eraxis 50 mg to be administered as directed | |

2. Results:

One respondent of the inpatient prescription study interpreted the proposed name as Enoxin. Enoxin is the proprietary name for enoxacin tablets which is a currently marketed Australian quinolone antibiotic.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Eraxis, the primary concerns related to look-alike and sound-alike confusion with Evoxac, Eurax Cream and Lotion, Plenaxis, Errin, and Uracid.

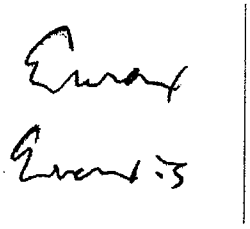
Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Eraxis could be confused with Enoxin. Enoxin is the proprietary name for, enoxacin tablets which is a currently marketed Australian quinolone antibiotic. DMETS did not review this product further due to numerous differentiating product characteristics such as the product strength, indication for use, frequency of administration, route of administration and dosage formulation. Since Enoxin is not marketed in this country, there will be minimal potential for error.

1. Evoxac may sound similar to Eraxis when spoken and look similar when scripted. Evoxac is Cevimilin Hydrochloride, indicated for the treatment of symptoms of dry mouth in patients with Sjögren's syndrome. The usual adult dosage of Evoxac is 30 mg three times daily. Evoxac is available in capsules for oral administration. Evoxac owes sound-alike properties to the shared letter "E" to begin each name, the "x" in the middle, and shared number of syllables (3) with Eraxis. However, the "v" sound and ending consonant "ac" in Evoxac may differentiate the names phonetically. Look-alike similarities between Evoxac and Eraxis may be attributed to similar name length and the shared letters "E" and "x". The letters "vo" in Evoxac may also look like the "ra" in Eraxis (see writing sample at the top of page 6).

Eurax
Evoxac

Despite some phonetic and orthographic similarities, Evoxac and Eraxis have many product differences including, route of administration (oral vs. intravenous), dosage form (capsule vs. for injection), strength and dose (30 mg vs. 50 mg), dosing regimen (three times daily vs. once daily), and indication of use (prevention of dry mouth vs. against esophageal candidiasis), respectively. Product differences and lack of convincing sound-alike/look-alike properties will minimize the potential for error.

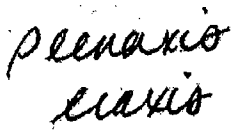
2. Eurax may sound similar to Eraxis when spoken and look similar when scripted. Eurax is crotamiton, indicated for eradication of scabies (*Sarcoptes scabiei*) and for symptomatic treatment of pruritic skin. The usual dosage of Eurax is to apply it to the body, chin down followed by an additional application 24 hours later. Eurax is available in cream and lotion dosage forms for topical administration. Eurax owes sound-alike properties with Eraxis primarily to the "rax" sound in the middle of the names. However, the different-sounding "Eu" sound beginning Eurax and the additional syllable "is" ending in Eraxis may serve to differentiate the names phonetically. Look-alike similarities between Eurax and Eraxis may be attributed to the shared letters "E", "r" and "x". The name pair also has the letter "a" in common but its placement is different. Differences in name length, the different placement of the "x", and the "i" in Eraxis may serve to differentiate the names orthographically (see writing sample below).



Despite some phonetic and orthographic similarities, Eurax and Eraxis have many product differences including, route of administration (topical vs. intravenous), dosage form (cream or lotion vs. for injection), strength (10% vs. 50 mg), and indication of use (against scabies vs. against esophageal candidiasis), respectively. Product differences and lack of convincing sound-alike and look-alike properties will minimize the potential for error.

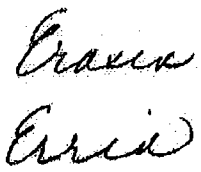
3. Plenaxis may sound similar to Eraxis when spoken and look similar when scripted. Plenaxis is abaralix, indicated for the palliative treatment of men with advanced symptomatic prostate cancer in whom LHRH agonist therapy is not appropriate, who refuse surgical castration, and have one or more of the following: 1) Risk of neurological compromise because of metastases, 2) ureteral or bladder outlet obstruction caused by local encroachment or metastatic disease, or 3) severe bone pain from skeletal metastases persisting on narcotic analgesia. The usual dosage of plenaxis is 100 mg intramuscularly to the buttock on days 1, 15, 29 (week 4), and every 4 weeks thereafter. Plenaxis is available as 100 mg "for injection" vials. Plenaxis owes sound-alike properties to the "axis" sound to end the names. However, the "Plen" sound beginning Plenaxis and the "r" sound in Eraxis may serve to differentiate the names phonetically. Look-alike similarities

between Plenaxis and Eraxis may be attributed to the ending letters "enaxis" vs. "eraxis", respectively, where the "n" and "r" may look similar. However, the "Pl" beginning Plenaxis and the differences in name length may serve to differentiate the names orthographically (see writing sample below).



Along with some phonetic and orthographic similarities, Plenaxis and Eraxis have product similarities in that they share dosage form (for injection). The products may also overlap on dose, since the usual initial dose for Eraxis, 100 mg, is also the usual adult dose of Plenaxis. Dose confusion may be averted, however, if the prescriber includes the Eraxis maintenance dose (100 mg loading dose followed by 50 mg daily thereafter). Plenaxis and Eraxis also have product differences including strength (100 mg vs. 50 mg), dosing schedule (days 1, 15, 29 (week 4), and every 4 weeks thereafter vs. once daily), and indication of use (against prostate cancer vs. against esophageal candidiasis), respectively. Additionally, for safety reasons, Plenaxis is approved with marketing restrictions. Plenaxis will be provided to physicians enrolled in the Plenaxis PLUS Program[5]. Limited Plenaxis distribution will serve as an additional barrier to product confusion. Product differences, limited Plenaxis distribution, and lack of convincing sound-alike and look-alike properties will minimize the potential for error.

4. Errin may look similar to Eraxis when scripted. Errin is norethindrone, indicated for prevention of conception. The usual dosage of Errin is one tablet daily. Errin owes look-alike properties with Eraxis to the shared letters "Er" and "i". However, the distinctive "x" in Eraxis may serve to differentiate the names orthographically (see writing sample below).

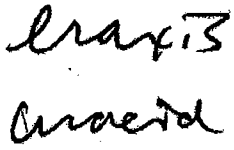


Despite some orthographic similarities, Errin and Eraxis have many product differences including, route of administration (oral vs. intravenous), dosage form (tablet vs. for injection), strength and dose (0.35 mg vs. 50 mg), practice settings (outpatient use vs. inpatient use), and indication of use (to prevent pregnancy vs. against esophageal candidiasis), respectively. Product differences and lack of convincing look-alike properties will minimize the potential for error.

5. Uracid may sound similar to Eraxis when spoken and look similar when scripted. Uracid is methionine, indicated for control of odor, dermatitis and ulceration caused by ammoniacal urine in incontinent adults. The usual dosage of Uracid is one capsule three to four times daily after meals. Uracid owes sound-alike properties with Eraxis to the

[5] Web Reference: http://www.plenaxisplus.com

shared number of syllables (3), and letters "ra" and "i". The "Er" in Eraxis may sound like the "Ur" in Uracid as can the "xi" and "ci" sounds. However, the "s" sound ending Eraxis is distinctive compared to the "d" sound ending Uracid and may serve to differentiate the names phonetically. Look-alike similarities between Uracid and Eraxis may also be attributed to the shared letters "ra" and "i". However, the upstroke of the "d" in Uracid may serve to differentiate the names orthographically (see writing sample below).



Despite some phonetic and orthographic similarities, Uracid and Eraxis have many product differences including, route of administration (oral vs. intravenous), dosage form (capsule vs. for injection), strength and dose (200 mg vs. 50 mg), dosing regimen (three to four times daily vs. daily), and indication of use (against urinary odor and dermatits vs. against esophageal candidiasis), respectively. Product differences and lack of convincing sound-alike and look-alike properties will minimize the potential for error.

E. [ ] NAME ANALYSIS

The analysis conducted by [ ] discusses the following names that were not identified as potential sound or look-alike products by DMETS, Afaxin, Alaxin, Aralis, Arixtra, Atarax, Avaxim, Axid, Brexin, Cefixime, Droxia, Duraxin, Efacin, Efasin, Eltroxin, Enarax, Eradacil, Eramycin, Erex, Ergamisol, Ervahist, Erymax, Esidrix, Filaxis, Geravim, Lasix, Mabasin, Oracit, Oraqix, Perazil, Permax, Peroxin, Ralix, Raxar, Restasis, Serax, Survanta, Teramin, Theracsy, Therahist, Vertavis, Xigris, Zebrax, and Zeroxin. Following review of the proprietary name analysis submitted by [ ] DMETS concurs that none of the aforementioned names poses a significant safety risk due to lack of lack of convincing sound-alike and look-alike properties and product differences. Additionally, DMETS acknowledges that the following products have been discontinued, thereby further decreasing the potential for error: Alaxin, Aralis, Brexin, Perazil, Raxar, Teramin, Therahist, Vertavis, and Zeroxin. We concur with the overall findings of the study.

## III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Eraxis, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT

Please change all "(w/w) ethanol" to "(w/w) Dehydrated Alcohol, USP".

B. CONTAINER LABEL (Eraxis for Injection)

1. See GENERAL COMMENT IIIA.

2. Add the quantitative information for fructose, etc., on the container label.

3. Relocate the strength to immediately follow the statement of identity.

4. Since the top left corner contains the statement, "1 Single-use Vial", delete the statement, [redacted], appearing on the principal display panel. It is redundant and takes label space.

5. Revise the route of administration to read,

**For Intravenous Infusion Only**
after reconstitution and further dilution

Please note that the abbreviation "IV" has been spelled out (intravenous). Through postmarketing experience DMETS is aware of misinterpretations of the abbreviation "IV".

6. Delete the asterisk appearing on the strength.

7. Relocate the asterisked statement, "When reconstituted...anidulafungin.", to appear in the "RECONSTITUTION", section and revise to read,

**"RECONSTITUTION: Eraxis must be reconstituted with 15 mL supplied diluent. Each mL contains 50 mg/15 mL (3.3 mg anidulafungin). Further dilute to 0.5mg/mL with ...infusion."**

C. CONTAINER LABEL (Diluent 15 mL)

1. See GENERAL COMMENT IIIA.

2. See comments 4 and 5 for CONTAINER LABEL (Eraxis for Injection), Section IIIB.

3. Change the vial label from "Diluent" to "Sterile Diluent for Eraxis".

4. Relocate "15 mL" to appear with "Single-use Vial", at the top of the principal display panel, and revise that statement to read, "15 mL Single Use Vial".

5. Increase the prominence of the statement, "Diluent to be used with Eraxis (anidulafungin) 50 mg", appearing on the side panel.

D. CARTON LABELING (Eraxis/Diluent)

1. See GENERAL COMMENT IIIA.

2. See comments 2, 3, 5, 6, and 7, for CONTAINER LABEL (Eraxis for Injection), Section IIIB.

3. Delete "Unit Pack" appearing with the route of administration.

4. Add the statement: "The rate of infusion should not exceed 1.1 mg/minute", as the last sentence in the **DOSAGE AND USE** section.

5. Delete the large, "50 mg", appearing to the right of the principal display panel and on the top panel.

6. Add "Unit Pack Contains:" to the statement of contents appearing at the top of panels to read,

Unit Pack Contains:
1 Single-use Vial Eraxis 50 mg
1 Single-use Diluent 15 mL

E. INSERT LABELING

1. DESCRIPTION

See GENERAL COMMENT IIIA, regarding nomenclature of alcohol.

2. HOW SUPPLIED

a. Include the complete established name of this product in the first sentence.

b. See GENERAL COMMENT IIIA, regarding nomenclature of alcohol.

Appendix A. Prescription Studies for Eraxis

| Verbal | Inpatient | Outpatient |
|---|---|---|
| Iraxis | Eraxir | Eraxis |
| Eraxis | Enaxin | Eraxis |
| Eraxis | Eraxin | Eraxis |
| Eraxis | Evaxin | Eraxis |
| Eraxis | Evaxin | Eraxis |
| Eraxis | Enoxin | Eraxis |
| Eraxis | Enaxir | Eraxis |
| Eraxis | Evaxin | Eraxis |
| Iraxis | Evaxin | Eraxis |
| Eraxus | Eraxin | Eraxis |
| Eraxus | Eraxin | Eraxis |
| Eraxis | Evaxin | Eraxis |
| Eraxis | Eraxin | Eraxis |
| Iraxis | Eraxin | Eradis |
| Eraxis | Eraxin | Eraxis |
| Eraxis | | Eraxis |
| Eraxis | | Eraxis |
| Eraxis | | Eraxis |
| Eraxis | | Eraxis |
| Eraxis | | Eraxis |
| Eraxis | | Eraxis |
| Elexist | | Eraxis |
| | | Eraxis |
| | | Eraxis |
| | | |
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| | | |

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/s/

Charles Hoppes
2/13/2006 11:20:37 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
2/13/2006 01:29:43 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/13/2006 02:31:50 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, DMETS Director, in her absence

---

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/s/

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Kristen Miller
2/16/2006 04:00:34 PM
CSO

Owen McMaster
2/16/2006 04:23:52 PM
PHARMACOLOGIST

William Taylor
2/17/2006 06:54:30 AM
PHARMACOLOGIST

**MEMORANDUM OF MEETING MINUTES**

| | |
|---|---|
| **MEETING DATE:** | February 3, 2006 |
| **APPLICATION:** | NDA 21-632 |
| | NDA 21-948 |
| **DRUG NAME:** | Eraxis® (anidulafungin) |
| **TYPE OF MEETING:** | Telecon: Pharmacology Toxicology Labeling |

**PFIZER ATTENDEES:**

Leigh-Ann Burns-Naas, Worldwide Safety Sciences
Maureen Garvey, Regulatory
Beth Goldstein, Vicuron, Director of Microbiology
Justine King, Regulatory
Haran Schlamm, Clinical

**FDA ATTENDEES:**

William Taylor, Ph.D. Pharmacology Toxicology Team Leader (DSPTP)
Owen McMaster, Ph.D. Pharmacology Toxicology Reviewer (DSPTP)
Kristen Miller, Pharm.D., Regulatory Project Manager (DSPTP)

**BACKGROUND:**

New drug applications 21-632 and 21-948 for Eraxis (anidulafungin) will be approved on February 17, 2006. Three reports of Ames bacterial reverse mutation assays with anidulafungin were submitted. In toxicology report #8, two drug lots tested positive in the Ames assay. Pfizer retested those two lots and they were again positive. Multiple HPLC peaks were observed in these lots and Pfizer believes the lots had contamination. Several other lots of drug, including clinical lots and crude starting material, tested negative in the Ames assay. This teleconference was scheduled to further discuss this finding, and to discuss the pharmacology/toxicology sections of the Eraxis labeling.

**DISCUSSION POINTS:**

Following introductions, Pfizer provided additional background regarding the Ames tests. Dr. McMaster expressed his appreciation for the elegant experiments Pfizer conducted to investigate the differing results; however, he stated that the sponsor has not fully resolved the conflicting assay results. Specifically, Agency regulations require that genotoxicity studies should be conducted according to Good Laboratory Practices (GLP) and several of the studies that had negative findings were not. In particular, several of the drug lots used in the assays with the negative findings were not characterized. Pfizer asserted that the contamination was microbial, and referred to a personal communication as proof of this microbial contamination; however, proof of microbial contamination was not substantiated by their submission.

Dr. McMaster recommended that Pfizer conduct a GLP Ames assay using a characterized drug batch produced as it will be produced for clinical use. If this GLP study does not

produce evidence of genotoxic potential for anidulafungin, then the label can be updated to reflect these findings. Dr. McMaster proposed that wording to reflect the current results in the labeling would be worked out over the next several days.

Dr. McMaster then asked if Pfizer had investigated how this contamination could have occurred and if action had been taken to prevent clinical lots from becoming contaminated. Pfizer stated that sterility testing was being done on the drug substance and drug product.

Finally, Dr. McMaster requested the following labeling changes and Pfizer agreed to make the changes:

In the last sentence of the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection of **PRECAUTIONS**, Pfizer should include the maximum dose used.

The **ANIMAL PHARMACOLOGY AND TOXICOLOGY** section was revised as follows:
In 3-month studies, liver toxicity, including single cell hepatocellular necrosis, hepatocellular hypertrophy and increased liver weights [ ] -were observed in monkeys and rats [ ] five to six times human exposure [ ]

Dr. Taylor stated that the information proposed by the sponsor in the reproductive toxicology section was to his satisfaction.

**Minutes Preparer:** Kristen Miller, Pharm.D., Project Manager
**Concurrence:** Owen McMaster, Ph.D., Pharmacology Toxicology Reviewer
**Concurrence:** William Taylor, Ph.D., Pharmacology Toxicology Team Leader

**MEMORANDUM**

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

**Date:** February 2, 2006

**To:** NDAs 21-632 and 21-948/ Pfizer Pharmaceuticals

**From:** Kristen Miller, DSPTP

**Subject:** DDMAC review of the name Eraxis

DDMAC objects [

]

Please note that 21 CFR 201.10(c)(3) states that a proprietary name that implies that the drug or ingredient has some unique effectiveness or composition would be misleading, if the drug or ingredient is a common substance, the limitations of which are readily recognized when the drug or ingredient is listed by its established name. In addition, the statute also provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

**MEMORANDUM**

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/s/
---
Kristen Miller
2/2/2006 09:13:11 AM
CSO

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

# REQUEST FOR CONSULTATION

TO *(Division/Office)*:
**irector, Division of Medication Errors and**
**echnical Support (DMETS), HFD-420**
**WO22, RM 4447**

FROM: Renata Albrecht, MD
Director
Division of Special Pathogen and Transplant Products

| DATE | IND NO. | NDA NO. | TYPE OF DOCUMENT | DATE OF DOCUMENT |
|---|---|---|---|---|
| 12/15/05 | | 21-632<br>21-948 | Request for tradename review | 12/2/05 |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| anidulafungin | High | antifungal | 2/1/06 |

NAME OF FIRM: Pfizer, Inc

**REASON FOR REQUEST**

**I. GENERAL**

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

**II. BIOMETRICS**

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| ☐ TYPE A OR B NDA REVIEW<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☐ OTHER (SPECIFY BELOW): | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ OTHER (SPECIFY BELOW): |

**III. BIOPHARMACEUTICS**

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

**IV. DRUG EXPERIENCE**

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

**V. SCIENTIFIC INVESTIGATIONS**

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: NDA 21-632 (AE Action, waiting for resubmission) and 21-948 (under review) were submitted by Vicuron Pharmaceuticals, and the name [redacted] was approved by DMETS. Since then, the applications were bought by Pfizer, who is requesting a change in the established name from [redacted] to ERAXIS. The Division would like to take an action on both applications on February 18, 2006, due date for NDA 21-948; Therefore, we are requesting expedited review of this tradename. Hard copy will be delivered to DMETS.

**PDUFA DATE: 2/18/06**
**ATTACHMENTS:** Draft Package Insert, Container and Carton Labels
**CC:** Archival IND/NDA 21-632 and 21-948
HFD- /Division File
HFD- /RPM
HFD- /Reviewers and Team Leaders

| NAME AND PHONE NUMBER OF REQUESTER | METHOD OF DELIVERY (Check one) |
|---|---|
| Judit Milstein, CPMS, DSPTP, 301796-0763 | ☐ DFS ONLY ☐ MAIL ☒ HAND |
| SIGNATURE OF RECEIVER | |

| | |
|---|---|
| | SIGNATURE OF DELIVERER |

5/28/05

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/s/

Judit Milstein
12/15/2005 11:38:55 AM
NDA 21-632 and 21-948 Request for ERAXIS tradename review

# NDA REGULATORY FILING REVIEW
**(Including Memo of Filing Meeting)**

NDA # 21-948 Supplement # SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: [illegible]
Generic Name: anidulafungin
Strengths: 50 mg

Applicant: Vicuron Pharmaceuticals Inc.

Date of Application: August 18, 2005
Date of Receipt: August 18, 2005
Date clock started after UN:
Date of Filing Meeting: September 27, 2005
Filing Date: October 17, 2005
Action Goal Date (optional): User Fee Goal Date: February 17, 2006

Indication(s) requested: Treatment of candidemia and other forms of invasive candidiasis.

Type of Original NDA: (b)(1) __X__ (b)(2) _____
OR
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 is a (b)(2), complete Appendix B.*

*(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

__X__ NDA is a (b)(1) application OR ___ NDA is a (b)(2) application

Therapeutic Classification: S _____ P 7030410 (Systemic Antifungal)
Resubmission after withdrawal? NO Resubmission after refuse to file? NO
Chemical Classification: (1,2,3 etc.) 6
Other (orphan, OTC, etc.) N/A

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

User Fee Status: Paid ____X____ Exempt (orphan, government)

Waived (e.g., small business, public health)

User Fee ID# PD3006115

Clinical Data [YES] NO

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES

  [NO]

  If yes, explain:

- 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)]? [N/A] 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? [N/A] YES

  NO

- Does the submission contain an accurate comprehensive index? [YES]

  NO

- 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:

- If an electronic NDA, does it follow the Guidance? N/A YES
  NO
  **If an electronic NDA, all certifications must be in paper and require a signature.**
  Which parts of the application were submitted in electronic format?

1 Table of Contents (Index)

2 Labeling

3 Summary

4 Chemistry

5 Nonclinical Pharmacology & Toxicology

6 Human Pharmacology & Bioavailability/Bioequivalence

7 Clinical Microbiology

8 Clinical

9 SafetyUpdate Report

10 Statistical

11 Case Report Tabulations

12 Case Report Forms

13 Patent Information

14 Patent Certification

15 Establishment Description

16 Debarment Certification

17 Field CopyCertification

18 User Fee Cover Sheet

19 Financial Disclosure

20 Other
May 21, 2004 FDA Approvable
Action Letter

Additional comments:

- If in Common Technical Document format, does it follow the guidance? [N/A] YES NO

- Is it an electronic CTD? N/A YES [NO]
**If an electronic CTD, all certifications must be in paper and require a signature.**
Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information submitted on form FDA 3542a? [YES] NO

- Exclusivity requested? YES, _____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 . . . ."*

- Financial Disclosure forms included with authorized signature? [YES] NO
**(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)**

- Field Copy Certification (that it is a true copy of the CMC technical section)? [YES] NO
Note: Electronically submitted, field has access to electronic copy

**Refer to 21 CFR 314.101(d) for Filing Requirements**

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

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. [YES] NO

- List referenced IND numbers: 54,597 and

- End-of-Phase 2 Meeting(s)? Date(s) _____ [NO]
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ [NO]

If yes, distribute minutes before filing meeting.

## Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  [YES] NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? [YES] NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? [N/A] YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  [N/A] YES NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? [N/A] YES NO
- Has DOTCDP been notified of the OTC switch application? [N/A] YES NO

## Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  [N/A] 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 Florian Zielinski (HFD-357)? YES
  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? [YES] NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? [YES] NO

ATTACHMENT

## MEMO OF FILING MEETING

DATE: October 17, 2005

BACKGROUND:
NDA 21-632, [ ] (anidulafungin) for Injection, was submitted on April 25, 2003 for initial treatment of esophageal candidiasis. An approval letter that issued on May 21, 2004 for this NDA stated:

A satisfactory risk-benefit ratio for the use of anidulafungin in the treatment of esophageal candidiasis has not been demonstrated. Clinical studies demonstrated a possible signal for hepatotoxicity, and the esophageal candidiasis study (VER002-4) demonstrated that anidulafungin has a higher relapse rate at the two-week post therapy visit than the comparator therapy. Even without the safety concern, the results of the single pivotal esophageal candidiasis study do not support the use of anidulafungin as initial therapy for esophageal candidiasis because of the high relapse rate at the two-week post therapy visit.

This deficiency may be addressed by providing the following:

In order to address the concern regarding hepatic toxicity you must provide additional clinical data to further characterize the safety of anidulafungin. This information should be from clinical studies evaluating anidulafungin at doses and durations that equal or exceed the esophageal candidiasis regimen.

In order to address the concern regarding the efficacy of anidulafungin, you must provide additional clinical data to address the observed high relapse rate and/or provide supportive evidence of anidulafungin's efficacy as an anti-candidal agent. This concern may be addressed by submitting results from one or both of the following types of studies:

- An adequate and well- controlled study evaluating alternative regimens of anidulafungin to reduce the relapse rates in patients with esophageal candidiasis. This study would need to demonstrate both efficacy at the end of therapy and durability of response at the two-week follow-up visit to support the labeling of anidulafungin as initial therapy in esophageal candidiasis.

AND/OR

- An adequate and well- controlled study demonstrating the efficacy of anidulafungin in another infection due to *Candida* spp. This study would provide supportive evidence of anidulafungin's efficacy as an anti-candidal agent; however, it would not support labeling of anidulafungin as initial therapy in esophageal candidiasis because this type of study would not address the high relapse rate observed in study VER002-4.

In order to garner an indication for esophageal candidiasis, you will need to provide additional efficacy data as described above and also demonstrate an acceptable overall safety profile for anidulafungin, including the results of the additional clinical safety data submitted in response to this letter.

We strongly encourage you to discuss with us these options and how these deficiencies could be addressed.

Alternatively, you could develop and seek approval for anidulafungin for more serious antifungal infections (such as candidemia and invasive candidiasis) or for patients who have fewer therapeutic options (such as those with refractory *Candida* infections and/or intolerant of other products). A safety profile not acceptable in a less serious disease may be tolerated if efficacy is demonstrated in a more serious disease or for those with fewer therapeutic options.

NDA 21-948, submitted August 18, 2005, contains study VER002-9B entitled "A Phase 3, Double-Blind, Randomized, Multi-Center, Study of the Safety and Efficacy of Anidulafungin vs. Fluconazole in the Treatment of Patients with Candidemia and Other Forms of Invasive Candidiasis and Prevention of Complications." This study was submitted to address the following from the May 21, 2003 approvable letter to NDA 21-632:

- An adequate and well- controlled study demonstrating the efficacy of anidulafungin in another infection due to *Candida* spp. This study would provide supportive evidence of anidulafungin's efficacy as an anti-candidal agent; however, it would not support labeling of anidulafungin as initial therapy in esophageal candidiasis because this type of study would not address the high relapse rate observed in study VER002-4.

ATTENDEES: Albrecht, Renata; Gitterman, Steven; Milstein, Judit ; Willard, Diana M; Colangelo, Philip M; Bala, Shukal; Higgins, Karen M; O'Shaughnessy, Elizabeth; Sacks, Leonard V; Chilukuri, Dakshina; Steele-Moore, Lynn; Dixon, Cheryl A; Seggel, Mark R; Duggan II, Donovan F; Cavaille Coll, Marc W; Goldberger, Mark J; Cox, Edward M; Roeder, David L

ASSIGNED REVIEWERS:

| **Discipline** | **Reviewer** |
|---|---|
| Medical: | O'Shaughnessy |
| Secondary Medical: | Cavaille-Coll |
| Statistical: | Dixon |
| Pharmacology: | McMaster |
| Statistical Pharmacology: | |
| Chemistry: | Seggel |
| Environmental Assessment (if needed): | |
| Biopharmaceutical: | Chilikuri |
| Microbiology, sterility: | |
| Microbiology, clinical (for antimicrobial products only): | Moore |
| DSI: | |
| Regulatory Project Management: | Duggan |
| Other Consults: | |

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

CLINICAL FILE __X____ REFUSE TO FILE

_____

- Clinical site inspection needed: Site 41(It is the largest site in the study (25 total patients) and it appears that this site is driving the statistical superiority. This site had a 93% success rate (14/15) for anidulafungin compared to a 50% success rate (5/10) for fluconazole.) [YES] NO

- 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 NA _____ FILE __X__ REFUSE TO FILE _____

STATISTICS FILE __X__ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE __X__ REFUSE TO FILE _____

- Biopharm. inspection needed: YES NO

PHARMACOLOGY NA _____ FILE __X__ REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE __X__ REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

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

__X__ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. 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.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Regulatory Project Manager, HFD-590
Version: 6/16/2004

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/s/

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Don Duggan
11/30/2005 10:03:47 AM
CSO

**Deputy Office Director and Division Director Review #3**

| | |
|---|---|
| **APPLICANT:** | **Pfizer** |
| **DRUG:** | **Anidulafungin** |
| **TRADE NAME:** | **Eraxis™ for Injection** |
| **NDA:** | **21-948 & 21-632** |
| **DATE OF SUBMISSION:** | **August 18, 2005** |
| **PDUFA GOAL DATE:** | **February 18, 2006** |
| **FORMULATION:** | **Intravenous injection (50 mg/vial)** |
| **INDICATION:** | **Candidemia and** and other forms of *Candida* infections (intra-abdominal abscess and peritonitis)<br>**Esophageal Candidiasis** |
| **RELATED MATERIAL:** | **NDA 21-632 (esophageal candidiasis)**<br>**Original Reviews: Drs Imo Ibia, Cheryl Dixon, Owen McMaster**<br>**Original Acting Office Director and Division Director Reviews (#1 and #2)**<br>**Approvable letters: May 21, 2004 and November 25, 2005**<br>**ODS Consult, Dr John Senior**<br>**NDA 21-948 (candidemia and invasive candidiasis)**<br>**Medical Review, Dr Elizabeth O'Shaughnessy**<br>**Statistical Review, Dr Cheryl Dixon**<br>**Microbiology Review, Lynn Steele Moore** |

---

## A. RECOMMENDATIONS:

An approval letter for both NDA's should be issued and anidulafungin should be approved for both of the following indications.

- Candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis). (see CLINICAL STUDIES and MICROBIOLOGY). ERAXIS has not been studied in endocarditis, osteomyelitis, and meningitis due to *Candida*, and has not been studied in sufficient numbers of neutropenic patients to determine efficacy in this group. [NDA 21-948]

- Esophageal candidiasis (see CLINICAL STUDIES, see Table 7 for higher relapse rates off anidulafungin therapy). [NDA 21-632]

Labeling has been discussed and both indications are included in one package insert for the anidulafungin IV product. The esophageal candidiasis application previously received an approvable on November 25, 2005, pending final negotiation of labeling.

Although the candidemia study showed statistical superiority, in order for the company to be able to claim superiority of the product, a second study confirming superiority would need to be submitted. This policy was discussed with Pfizer during labeling discussions. No claim of drug superiority is included in the labeling.

**Phase 4 studies**

Pediatric studies of candidemia are deferred until 2011. Pediatric studies of esophageal candidiasis are waived because the higher relapse rate after anidulafungin therapy does not constitute a meaningful therapeutic benefit and the number of patients is small. This is consistent with the criteria stated in the PREA legislation.

## B. SUMMARY OF NDA 21-948

The applicant (originally Vicuron, now Pfizer) submitted results of study VER002-9, the comparative study of anidulafungin and fluconazole in "candidemia and invasive candidiasis," as well as a Phase 2 dose-ranging study, VER002-6 and an open study VER002-9b in support of this indication. The dosage regimen in VER002-9 was a 200 mg loading dose followed by daily doses of 100 mg IV, twice the daily amount of anidulafungin compared to the recommended dosage regimen for the esophageal candidisis indication. The results of VER002-9 showed the anidulafungin regimen to be statistically superior to the comparative fluconazole regimen and the application was granted a priority review.

> Excerpt from MaPP 6020.3, Priority Review: The drug product, if approved, would be a significant improvement compared to marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis, or prevention of a disease. Improvement can be demonstrated by, for example: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness of a new subpopulation.

**Background Information:**

Anidulafungin is an echinocandin, a class of antifungal drugs that inhibits the synthesis of 1,3-β-D-glucan, an essential component of fungal cell walls. ERAXIS is a sterile, lyophilized product for intravenous (IV) infusion that contains anidulafungin. ERAXIS (anidulafungin) is a semi-synthetic lipopeptide synthesized from a fermentation product of *Aspergillus nidulans*. Anidulafungin is the third approved IV echinocandin drug product. To date Cancidas (caspofungin) and Mycamine (micafungin) have been approved for marketing in the US.

The pharmacokinetics following the 200 mg loading dose/100 mg daily maintenance dose approved for the candidemia indication and the 100 mg loading dose/50 mg daily maintenance dose approved for the esophageal candidiasis indication are provided in the table below:

**Mean (%CV) Steady State Pharmacokinetic Parameters of Anidulafungin Following IV Administration of Anidulafungin in Patients with Fungal Infections Estimated Using Population Pharmacokinetic Modeling**

| PK Parameter* | Anidulafungin IV Dosing Regimen (LD/MD, mg) | |
|---|---|---|
| | 100/50 | 200/100 |
| Cmax, ss (mg/L) | 4.2 (22.4) | 7.2 (23.3) |
| Cmin, ss (mg/L) | 1.6 (42.1) | 3.3 (41.8) |
| AUCss (mg·h/L) | 55.2 (32.5) | 110.3 (32.5) |
| CL (L/h) | 1.0 (33.5) | |
| t1/2, β (h)† | 26.5 (28.5) | |

* All the parameters were estimated by population modeling using a two-compartment model with first order elimination; AUCss, Cmax,ss and Cmin,ss (steady state trough plasma concentration) were estimated using individual PK parameters and infusion rate of 1 mg/min to administer recommended doses of 50 and 100 mg/day.

† t1/2, β is the predominant elimination half-life that characterizes the majority of the concentration-time profile.

After administration, anidulafungin undergoes slow chemical degradation. It is not a substrate, inducer, or inhibitor of cytochrome P450 (CYP450), does not significantly inhibit the activities of clinically important human CYP isoforms (1A2, 2C9, 2D6, 3A4) and showed no clinically relevant drug-drug interactions with the following drugs:

cyclosporine, tacrolimus, voriconazole, Ambisome, rifampin. Dosing adjustment is not needed in patients with either renal or hepatic impairment. These pharmacokinetic features make this drug useful for treatment of *Candida* infections in patients who are often on multiple other medications because of underlying diseases that predispose to *Candida* infections.

Anidulafungin is active *in vitro* against *Candida albicans, C. glabrata, C. parapsilosis, and C. tropicalis.* Of note, anidulafungin reduced the mycological burden of fluconazole-resistant *C. albicans* in an oropharyngeal/esophageal infection model in immunosuppressed rabbits, although there is insufficient clinical data to determine whether it is effective in the treatment of fluconazole-resistant isolates in patients.

The manufacturing process has been adequately described, storage and expiry determined, and no post-marketing commitments are needed. The company will monitor stability of the drug product and drug substance. ERAXIS (anidulafungin) is a lyophilized, preservative-free, powder, 50 mg anidulafungin is supplied in one vial. The companion second vial contains 15 mL of 20% (w/w) dehydrated alcohol in water for injection and serves as the single-use diluent.

**Efficacy Summary VER002-9, VER002-6 and VER002-9b: (see also review #2)**

The efficacy of ERAXIS was evaluated in a Phase 3 study **[VER002-9]**, a randomized, double-blind study of patients with candidemia and other forms of *Candida* infections (intra-abdominal abscess, and peritonitis). Patients were randomized to receive once daily IV ERAXIS (200 mg loading dose followed by 100 mg maintenance dose) or IV fluconazole (800 mg loading dose followed by 400 mg maintenance dose). Patients were stratified by APACHE II score (≤ 20 and > 20) and the presence or absence of neutropenia (≤500 and >500/mm$^3$). Patients with *Candida* endocarditis, osteomyelitis or meningitis, or those with infection due to *C. krusei,* were excluded from the study.

In this study, 256 patients constituted the ITT population; 131 received 100 mg IV anidulafungin, and 125 received 400 mg IV fluconazole for 14 to 42 days. Candidemia was present in more than 90% of patients in both study arms. Approximately half of all patients had invasive candidiasis related to an IV catheter (per investigator attribution). Most patients had a single baseline pathogen; *Candida albicans* was isolated in the majority of patients. Risk factors for candidemia among patients in both treatment arms in this study were: presence of a central venous catheter (78%), receipt of broad-spectrum antibiotics (69%), recent surgery (42%), recent hyperalimentation (25%), and underlying malignant condition (22%). The number of treated patients by country was USA (185), Canada (59), Belgium (2), Germany (3) Italy (6) and Netherlands (1). The largest number of patients (25) were enrolled at a single site in Canada. Patient disposition and reasons for discontinuation are presented below:

**Patient Disposition and Reasons for Discontinuation**

| | Treatment Group | |
|---|---|---|
| | Anidulafungin | Fluconazole |
| | N=131<br>n (%) | N=125<br>n (%) |
| Treated Patients | | |
| Patients completing study through 6 week follow-up | 94 (71.8) | 80 (64.0) |
| Deaths | 29 (22.1) | 39 (31.2) |
| Discontinuations From Study Medication, total | 34 (26.0) | 48 (38.4) |
| Discontinued due to adverse events | 12 (9.2) | 21 (16.8) |
| Discontinued due to lack of efficacy | 11 (8.4) | 16 (12.8) |

Demographic features were fairly balanced between the arms; some numeric differences were seen in Apache score, candidemia infection only, and use of immunosuppressive treatment, these do not account for the difference in efficacy (75.6% vs 60.2%, below).

| Selected Demographic and Baseline Characteristics (MITT) | | |
|---|---|---|
| | Treatment Group | |
| | Anidulafungin | Fluconazole |
| **# Patients** | N=127 | N=118 |
| | n (%) | n (%) |
| **Apache II Score** | | |
| ≤ 20 | 101 (79.5) | 98 (83.1) |
| > 20 | 26 (20.5) | 20 (16.9) |
| **Site of Infection** | | |
| Candidemia only | 116 (91.3) | 103 (87.3) |
| **Invasive Candidiasis Risk Factors** | | |
| Immunosuppressive therapy | 18 (14.2) | 27 (22.9) |

The primary objective was to determine if anidulafungin is at least as effective as fluconazole with respect to the global response (combined clinical and microbiological response at the end of IV therapy) for the treatment of patients with a diagnosis of candidemia and/or other forms of invasive candidiasis. The results for the primary endpoint, Global Response at End of IV Therapy, the results for additional analyses at secondary time points, and by pathogen response are summarized in the tables below:

| **Global Response at End of IV Therapy and Secondary Time Points in the Micro-ITT Population, VER002-9** | | | |
|---|---|---|---|
| **Time point** | **Anidulafungin** | **Fluoconazole** | **Between-Group Difference and CI*** ** |
| End of IV Therapy * | 96/127 (75.6) | 71/118 (60.2) | 15.4% (3.9 , 27.0) **(95%CI)** |
| End of Oral Therapy ** | 31/33 (93.9) | 28/33 (84.8) | 9.1% |
| End of All Therapy | 94/127 (74.0) | 67/118 (56.8) | 17.2% (2.9 , 31.6) **(98.3%CI)** |
| 2-Week Follow-Up | 82/127 (64.6) | 58/118 (49.2) | 15.4% (0.4, 30.4) **(98.3%CI)** |
| 6-Week Follow-Up | 71/127 (55.9) | 52/118 (44.1) | 11.8% (-3.4, 27.0) **(98.3%CI)** |

*The median duration of IV therapy was 14 and 11 days in the anidulafungin and fluconazole arms, respectively.
**33 patients in each arm (26% anidulafungin, 29% fluconazole) switched to oral fluconazole after the end of IV therapy. For those who received oral fluconazole, the median duration of oral therapy was 7 days for the anidulafungin arm and 5 days for the fluconazole arm.
***For the primary endpoint, the 95%CI was used, for the secondary endpoints the 98.3%CI was used to adjust for post hoc for multiple comparisons. Calculated ERAXIS minus fluconazole.

The superiority of the results is driven by study site 41 (Canada) which represents the highest enrolling site as well as the one with the greatest difference in efficacy between the two arms. When Site 41 is excluded from the analysis of the overall MITT population, the global response rate is 73.2% (82/112) for anidulafungin treated patients and 61.1% (66/108) for fluconazole treated patients. The 95% confidence interval about the difference of 12.1% is (-1.1, 25.3). A DSI inspection of the site, however, did not disclose any significant deviations from protocol. Furthermore, in subgroup analyses, it is reassuring to see that, while the Canadian site shows the greatest difference between the two arms, the other sites also consistently show that anidulafungin has numerically higher eradication compared to the control. It was noted that the fluconazole patients in the Canadian site were somewhat older than in the anidulafungin arm, but the analyses by age has too few patients to draw any conclusions.

Subgroup Analyses of Efficacy By Study Sites at End of IV therapy (MITT Population)

| | **Treatment Group** | |
|---|---|---|
| | **Anidulafungin** | **Fluconazole** |
| Overall outcome | 96/127 (75.6) | 71/118 (60.2) |
| **Country** | | |
| United States | 63/86 (73.3) | 55/90 (61.1) |
| Canada | 14/15 (93.3) | 5/10 (50) |
| Europe | 19/26 (73.1) | 11/18 (61.1) |

Per Dr Dixon's review

| | US | | non-US excluding 41 | | Site 41 | |
|---|---|---|---|---|---|---|
| | anidulafungin | fluconazole | anidulafungin | fluconazole | anidulafungin | fluconazole |
| **Age** | | | | | | |
| ≤ 65 | 34/51 (66.7) | 38/60 (63.3) | 16/21 (76.2) | 5/8 (62.5) | 12/12 | 2/4 |
| > 65 | 29/35 (82.9) | 17/30 (56.6) | 3/5 (30.0) | 6/10 (60.0) | 2/3 | 3/6 |

The mycological outcome by pathogen at the end of IV therapy is presented below

| **Global Success at End of IV Therapy by Pathogen (Micro-ITT Population), VER002-9** | | |
|---|---|---|
| | **Anidulafungin** | **Fluconazole** |
| **Baseline Species** | n/N (%) | n/N (%) |
| All species | 92/119 (77.3) | 65/106 (61.3) |
| *Candida albicans* | 60/74 (81.1) | 38/61 (62.3) |
| Non-*albicans* species | 32/45 (71.1) | 27/45 (60.0) |
| *Candida glabrata* | 9/16 (56.3) | 11/22 (50.0) |
| *Candida tropicalis* | 13/14 (92.9) | 4/8 (50.0) |
| *Candida parapsilosis* | 7/11 (63.6) | 10/12 (83.3) |
| *Candida guilliermondii* | 2/2 (100.0) | -- |
| *Candida krusei* | 0/1 (0.0) | -- |
| *Candida lusitaniae* | 1/1 (100.0) | 1/2 (50.0) |
| *Candida famata* | -- | 1/1 (100.0) |
| Note: N=Number of patients with a single baseline pathogen. | | |
| Source: Data from Section 14.2, Table 2.12. | | |

The following table presents outcome and mortality data for the MITT population and is included in the final labeling so that clinicians have a good perspective on the fact that the majority of the patients in this study had candidemia and did not have neutropenia. The information on site-specific infections is presented so that HCP can understand the limitations of the available data.

**Outcomes & Mortality in Candidemia and other *Candida* Infections**

| | **Anidulafungin** | **Fluconazole** | **Between group difference* ( 95% CI)** |
|---|---|---|---|
| **No. of MITT patients** | 127 | 118 | |
| | n/N (%) | n/N (%) | |
| **Favorable Outcomes (MITT) At End Of IV Therapy** | | | |
| **All MITT patients** | | | |
| **Candidemia** | 88/116 (75.9%) | 63/103 (61.2%) | 14.7 (2.5, 26.9) |
| Neutropenic | 1/2 | 2/4 | - |
| Non neutropenic | 87/114 (76.3%) | 61/99 (61.6%) | - |
| | | | |
| **Multiple sites** | | | |
| Peritoneal fluid/ intra-abdominal abscess | 4/6 | 5/6 | - |
| Blood/ peritoneum (intraabdominal abscess) | 2/2 | 0/2 | - |
| Blood /bile | - | 1/1 | - |
| Blood/renal | - | 1/1 | - |
| Pancreas | - | 0/3 | - |
| Pelvic abscess | - | 1/2 | - |
| Pleural fluid | 1/1 | - | - |
| Blood/ pleural fluid | 0/1 | - | - |
| Blood/left thigh lesion biopsy | 1/1 | - | - |
| Total | 8/11 (72.7%) | 8/15 (53.3%) | - |
| **Mortality** | | | |

| | | | |
|---|---|---|---|
| **Overall study mortality** | 29/127 (22.8 %) | 37/118 (31.4%) | - |
| Mortality during study therapy | 10/127 (7.9%) | 17/118 (14.4%) | - |
| Mortality attributed to *Candida* | 2/127 (1.6%) | 5/118 (4.2%) | - |

* Calculated as ERAXIS minus fluconazole

The results of this study were supported by (a) the results of the dose-ranging Phase 2 study **[VER002-6]** summarized in DD/OD review #1 and (b) data on 33 patients in a non-comparative study **[VER002-9b]** in which 21/31 (67.7%) had a successful outcome.

**Safety Summary VER002-9 (see also review #2)**

In this phase 3 study in patients received anidulafungin 200mg as a loading dose followed by 100 mg maintainance dose. A total of 256 patients were enrolled, 131 randomized to anidulafungin and 125 randomized to fluconazole.

Withdrawal from study medication was more frequent in the control arm. Withdrawal due to death occurred in 29 (22.1%) in the anidulafungin arm and 38 (30.4%) in the fluconazole arm before the 6 week follow up. In both the anidulafungin and fluconazole groups, cardiac arrest (2.9% anidulafungin, 5.6% fluconazole) was the most common AE resulting in death. There were no discernable patterns in the causes of death among anidulafungin-treated patients or between the anidulafungin and fluconazole treatment populations. A total of 12 patients (9.2%) on anidulafungin and 21 patients (16.8 %) on fluconazole withdrew for an adverse event. Withdrawal because of worsening clinical condition/lack of efficacy was seen in 11 (8.4%) anidulafungin and 16 (12.8%) fluconazole patients. No cases of QT prolongation occurred.

Hepatic Toxicity

Hepatic adverse events were more common in the fluconazole arm of the study. No cases of hepatic failure occurred. There were 5 (3.8%) patients in the anidulafungin group and 8 (6.3%) patients in the fluconazole group who reported clinical adverse events categorized under the hepatobiliary category. Four of these events were severe in intensity and all four occurred in fluconazole-treated patients. One hepatic AE that was considered possibly related to study drug occurred in an anidulafungin-treated patient (ongoing cholestasis in a patient with disseminated candidiasis). However, this case was confounded because both disseminated candidiasis and concomitant medications could have caused the hepatic abnormalities that were observed.

A comprehensive hepatic expert report was prepared by Dr. [redacted]
Vicuron's hepatic consultant, and concluded that anidulafungin posed a low risk of serious or life-threatening injury. The detailed evaluation of hepatic adverse events (applicant, their consultant, FDA) shows that there were hepatic events documented during the study, including patients who died and had derangement in hepatic laboratory tests and evidence of hepatitis. However, in essentially all of these patients, there was evidence of underlying medical conditions and/or the use of concomitant medications that either was responsible for the hepatic findings or where anidulafungin or fluconazole were not considered causative but an association with the use of the drug could not be excluded. Given these findings, and specifically the absence of any unconfounded cases where the study drug was the sole potential etiology for hepatic toxicity, the labeling for anidulafungin should carry the following information as the first paragraph in the PRECAUTIONS section of the labeling:

PRECAUTIONS

**Hepatic Effects**

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with ERAXIS. In some patients with serious underlying medical conditions who were receiving multiple concomitant medications along with ERAXIS, clinically significant hepatic abnormalities have occurred. Isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure have been reported in patients; a causal relationship to ERAXIS has not been established. Patients who develop abnormal liver function tests during ERAXIS therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing ERAXIS therapy.

Infusion Reactions

In animal studies, evidence of infusion reactions was seen, and characterized by swollen snout, red ears, ataxia, hypoactivity, thought to be evidence of histamine release and represent anaphylactoid reaction. These reactions occurred in the first few days of dosing.

In clinical studies, infusion reactions were also seen, but were relatively comparable between the two arms, As summarized in Dr. O'Shaughnessy's review, according to the applicant, a total of 28 (13.7%) anidulafungin and 9 (7.2%) fluconazole patients experienced infusion associated reactions, these were generally mild. In the table below, dyspnea is listed as an infusion reaction; however, a review of cases of dyspnea was conducted and, the majority of dyspnea cases in the clinical studies were attributable to underlying diseases (heart, pulmonary) and not infusion. Treatment with anidulafungin was continued in these patients. In the clinical database, most infusion reactions were characterized by flushing or local reactions. (see table below and Dr. O'Shaughnessey's review)

In a normal volunteer study, 2 subjects had dyspnea associated with infusion of anidulafungin, and infusion of the vehicle. After this Phase 1 study, the decision was made to limit infusion to 1.1 mg/minute to minimize the chance of infusion reactions.

There were 19 anidulafungin and 18 fluconazole patients who had hypotension during the treatment period but again these were considered to be related to patient's medical condition and not drug infusion.

In summary, although the labeling contains the statement, "Possible histamine-mediated symptoms have been reported with ERAXIS, including rash, urticaria, flushing, pruritus, dyspnea, and hypotension. These events are infrequent when the rate of ERAXIS infusion does not exceed 1.1 mg/minute." the clinical trial database has a few normal volunteers and patients who had dyspnea during infusion but it did not result in treatment discontinuation, and no patient had hypotension that was considered related to infusion and led to drug discontinutation. However, such events could be observed as part of a histamine reaction and therefore the labeling contains this statement.

**Possible Infusion-Associated Adverse Events: Phase 2-3 Integrated Database [Number (%) of Patients]**

| | Anidulafungin | | | Fluconazole | | |
|---|---|---|---|---|---|---|
| **AE Preferred Term** | **≤14 days (N=128)** | **>14 days (N=76)** | **Total (N=204)** | **≤14 days (N=90)** | **>14 days (N=35)** | **Total (N=125)** |
| **Patients with at least 1 infusion-associated AE** | 20 (15.6) | 8 (10.5) | 28 (13.7) | 5 (5.6) | 4 (11.4) | 9 (7.2) |
| Dyspnea | 16 (12.5) | 6 (7.9) | 22 (10.8) | 2 (2.2) | 2 (5.7) | 4 (3.2) |
| Flushing | 3 (2.3) | 1 (1.3) | 4 (2.0) | 2 (2.2) | 1 (2.9) | 3 (2.4) |
| Dyspnea exacerbated | 2 (1.6) | 0 | 2 (1.0) | 0 | 0 | 0 |
| Infusion related reaction | 0 | 1 (1.3) | 1 (0.5) | 1 (1.1) | 2 (5.7) | 3 (2.4) |
| Hot flush | 0 | 1 (1.3) | 1 (0.5) | 0 | 0 | 0 |

**Source:** Appendix A, Table 17-3. Includes data from studies VER002-6, VER002-9, and VER002-9b.
**Note:** Patients are only counted once at each level of summarization.

Anaphylaxis

There were no cases of anaphylaxis in this integrated analysis of safety or in the entire clinical program. A case of anaphylaxis due to caspofungin (Cancidas ™) has been reported in the published literature, (The Medical letter, 2001). For the two currently marketed echinocandins, FDA AERS has 3 reports of anaphylaxis for micafungin (Japanese reports) and 6 cases of anaphylaxis for caspofungin. If reports of anaphylaxis are reported post-marketing for anidulafungin, such information will be added to the product labeling.

The table below presents adverse events that were seen in ≥ 5% of the patients.

| **Adverse Events Experienced by ≥ 5% Patients in Either Study Arm, Study VER002-9** | | |
|---|---|---|
| | (ITT Population) | |
| | **Anidulafungin** | **Fluconazole** |
| | (N = 131) | (N = 125) |
| **Adverse Event** | n (%) | n (%) |
| Hypokalaemia | 33 (25.2) | 24 (19.2) |
| Nausea | 32 (24.4) | 15 (12.0) |

| | | |
|---|---|---|
| Diarrhoea | 24 (18.3) | 23 (18.4) |
| Bacteraemia | 23 (17.6) | 23 (18.4) |
| Pyrexia | 23 (17.6) | 23 (18.4) |
| Vomiting | 23 (17.6) | 12 (9.6) |
| Insomnia | 20 (15.3) | 12 (9.6) |
| Urinary tract infection | 19 (14.5) | 22 (17.6) |
| Hypotension | 19 (14.5) | 18 (14.4) |
| Alkaline phosphatase increased | 15 (11.5) | 14 (11.2) |
| Hypomagnesaemia | 15 (11.5) | 14 (11.2) |
| Hypertension | 15 (11.5) | 5 (4.0) |
| Dyspnoea | 15 (11.5) | 4 (3.2) |
| Oedema peripheral | 14 (10.7) | 16 (12.8) |
| Pleural effusion | 13 (9.9) | 11 (8.8) |
| Deep vein thrombosis | 13 (9.9) | 9 (7.2) |
| Anaemia | 12 (9.2) | 20 (16.0) |
| Constipation | 11 (8.4) | 14 (11.2) |
| Headache | 11 (8.4) | 10 (8.0) |
| White blood cell count increased | 11 (8.4) | 3 (2.4) |
| Confusional state | 10 (7.6) | 10 (8.0) |
| Sepsis | 9 (6.9) | 11 (8.8) |
| Hypoglycaemia | 9 (6.9) | 10 (8.0) |
| Cough | 9 (6.9) | 7 (5.6) |
| Pneumonia | 8 (6.1) | 19 (15.2) |
| Abdominal pain | 8 (6.1) | 16 (12.8) |
| Hyperkalaemia | 8 (6.1) | 14 (11.2) |
| Hyperglycaemia | 8 (6.1) | 8 (6.4) |
| Depression | 8 (6.1) | 5 (4.0) |
| Dehydration | 8 (6.1) | 2 (1.6) |
| Respiratory distress | 8 (6.1) | 2 (1.6) |
| Thrombocythaemia | 8 (6.1) | 1 (0.8) |
| Hepatic enzyme increased | 7 (5.3) | 14 (11.2) |
| Back pain | 7 (5.3) | 13 (10.4) |
| Decubitus ulcer | 7 (5.3) | 10 (8.0) |
| Chest pain | 7 (5.3) | 6 (4.8) |
| Leukocytosis | 7 (5.3) | 6 (4.8) |
| Blood creatinine increased | 7 (5.3) | 1 (0.8) |
| Anxiety | 6 (4.6) | 13 (10.4) |
| Rigors | 6 (4.6) | 11 (8.8) |
| Agitation | 6 (4.6) | 7 (5.6) |
| ALT increased | 6 (4.6) | 7 (5.6) |
| Staphylococcal bacteraemia | 6 (4.6) | 7 (5.6) |
| Cardiac arrest | 5 (3.8) | 11 (8.8) |
| Renal insufficiency | 5 (3.8) | 11 (8.8) |
| Renal failure acute | 5 (3.8) | 9 (7.2) |
| Hypothermia | 5 (3.8) | 8 (6.4) |
| Pulmonary oedema | 4 (3.1) | 13 (10.4) |
| Thrombocytopenia | 4 (3.1) | 13 (10.4) |
| Rash | 4 (3.1) | 11 (8.8) |
| Abdominal distension | 4 (3.1) | 8 (6.4) |
| Bradycardia | 3 (2.3) | 7 (5.6) |
| Dizziness | 3 (2.3) | 7 (5.6) |
| AST increased | 2 (1.5) | 9 (7.2) |
| Septic shock | 1 (0.8) | 10 (8.0) |
| Metabolic acidosis | 1 (0.8) | 7 (5.6) |
| Source: Data from Section 14.3, Table 3.7. | | |

**C: LABELING**

In labeling discussions with Pfizer, the Agency took into consideration (a) the findings in NDA 21-948 as well as NDA 21-632, esophageal candidiasis, (b) 21 CFR 201.57 – this NDA was submitted before the "Physician's Labeling Rule" became finalized, (c) the labeling for other approved echinocandins and antifungal products, (d) agency guidance documents on labeling. There were several specific issues important to the Agency and Pfizer that are summarized below.

The trade name, ERAXIS, was found acceptable by DMETS and objected to by DDMAC [ ]. This concern was not shared by the division, particularly in view of the results in the candidemia study and Pfizer will use this trade name. [Vicuron's trade name, [ ] was acceptable to FDA but was not adopted by Pfizer.]

The **CLINICAL PHARMACOLOGY** section includes data on the two approved adult dosage regimens; PK data from studies or lower and higher dosage regimens are also included to provide information on dose proportionality of anidulafungin and that $T_{1/2}$ and clearance do not vary significantly across the 3 doses, indicating that the PK of the drug is linear and/or stable. The table showing these results includes a footnote that safety and efficacy of these regimens has not been established, and also refers to the **OVERDOSAGE** section because there it states that 3 of 10 subjects at the higher dose(s) had elevations in LFTs.

The table of pediatric PK data in patients 2-11 years old is included because the data are considered robust and provide a comparison to adult PK parameters. This information is considered useful information for physicians who may need to use an antifungal in pediatric patients, given the limited available therapies. The limitations of pediatric clinical data are presented in **PRECAUTIONS: Pediatric Use:** "Safety and effectiveness of anidulafungin in pediatric patients has not been established. (see CLINICAL PHARMACOLOGY-Special Populations/Pediatric)"

The **Microbiology** section only includes information on *Candida* species. Although *in vitro* data were provided for other fungi, they are not included because there is no corresponding evidence of clinical efficacy from adequate and well controlled clinical studies.

In the **INDICATIONS AND USAGE** section, the wording for these indications was specifically chosen to communicate what patients were studied and outcome. Therefore, the indication is Candidemia and other forms of *Candida* infections (intra-abdominal abscess, and peritonitis) and not "invasive candidiasis" specifically because conditions that would be considered representative such as hepatosplenic candidiasis, endophthalmitis, endocarditis, osteomyelitis, and meningitis were not studied. Only 4 patients with neutropenia were enrolled, again an insufficient number to support any labeling statement.

As far as the Esophageal candidiasis indication, the two options considered were to state that anidulafungin (at the tested regimen) should not be used a first-line therapy or, that the relapse rates were higher after completing anidulafungin treatment. The latter statement was considered more correct and informative; and the **DOSAGE AND ADMINISTRATION** specifies that after EC treatment, it may be appropriate to consider suppressive therapy.

The **CLINICAL STUDIES** section was initially moved to the end of the labeling in accordance with 21 CFR 201.57. Pfizer correctly pointed out that recent approvals have included it near the **INDICATIONS AND USAGE** section, which would be their preference and agreed to move it when a consistent policy is applied across all product labeling.

In negotiating wording for the **CLINICAL STUDIES** section, there was a substantial amount of discussion how to report the results of the candidemia and other forms of *Candida* infection study. The study showed statistical superiority of anidulafungin over fluconazole, and the 95% CI included in the Table (above) excludes zero. However, the other controlled study (Phase 2 dose-ranging study) did not include an active control and thus did not corroborate superiority. Therefore, the company did not include any statements of superiority in the labeling.

The issue of superiority claims is addressed in the document *Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products (Content and Format).* The guidance was published with the *Physician Labeling Rule* in January 2006, is available at http://www.fda.gov/cder/regulatory/physLabel/default.htm and states:

> "If effectiveness can be determined only by comparison to an active control (superiority or non-inferiority trial) and the identity of the active comparator is important to a clinician's understanding of the drug's effects, the active control data and identity of the comparator should be included in labeling. In such cases, the labeling should make clear that no comparative claim has been established (if it has not been) and should disclose any limitations of the comparative data (e.g., if the comparator was administered in a suboptimal or unapproved regimen).
>
> "An explicit claim of superior or similar effectiveness must be supported by substantial evidence (21 CFR 201.56(a)(3)). For superiority claims, such evidence would include adequate and well-controlled trials designed to establish superiority of one treatment over another"

In the **PRECAUTIONS** section, the first section deals with Hepatic Effects in order that clinicians readily find this precautionary information. The wording for this section is essentially the same as wording in caspofungin and micafungin, because a thorough review of pre- and post-marketing cases for these drugs by both the Division and ODS show that the risk appears similar and includes underlying medical conditions and concomitant drugs.

The **ADVERSE REACTIONS** section does include events considered possibly, probably, or related to treatment. Although it is noted that other products have reported either treatment-emergent events or all events without regard to drug-relatedness, the anidulafungin labeling includes treatment-related events to be consistent with other echinocandin and antifungal package inserts.

The following tables show treatment related adverse events in the candidemia (study VER002-9) and esophageal candidiasis studies (study VER002-4).

**Treatment-related* adverse events reported in ≥2.0% of subjects receiving ERAXIS or fluconazole therapy for candidemia and other *Candida* infections**

| | **Anidulafungin 100 mg† N =131** | **Fluconazole 400 mg† N = 125** |
|---|---|---|
| | n (%) | n (%) |
| **Subjects with at least 1 treatment-related AE** | 32 (24.4) | 33 (26.4) |
| **Gastrointestinal System** | | |
| Diarrhea | 4 (3.1) | 2 (1.6) |
| **Investigations** | | |
| ALT ↑ | 3 (2.3) | 4 (3.2) |
| AST ↑ | 1 (0.8) | 3 (2.4) |
| Alkaline phosphatase ↑ | 2 (1.5) | 5 (4.0) |
| Hepatic enzyme ↑ | 2 (1.5) | 9 (7.2) |
| **Metabolic and Nutritional Systems** | | |
| Hypokalemia | 4 (3.1) | 3 (2.4) |
| **Vascular System** | | |
| Deep vein thrombosis | 1 (0.8) | 3 (2.4) |

*Treatment-related AEs are defined as those that are possibly or probably related to study treatment, as determined by the investigator.

| **Treatment-related adverse events reported in ≥1.0% of subjects receiving ERAXIS or fluconazole therapy for esophageal candidiasis** | | |
|---|---|---|
| | **Anidulafungin 50 mg† N = 300** | **Fluconazole 100 mg† N = 301** |
| | n (%) | n (%) |
| **Subjects with at least 1 treatment-related AE** | 43 (14.3) | 50 (16.6) |
| **Blood and lymphatic System** | | |
| Neutropenia | 3 (1.0) | -- |
| Leukopenia | 2 (0.7) | 4 (1.3) |
| **Gastrointestinal System** | | |
| Dyspepsia aggravated | 1 (0.3) | 3 (1.0) |
| Nausea | 3 (1.0) | 3 (1.0) |
| Vomiting NOS | 2 (0.7) | 3 (1.0) |
| **General Disorders and Administration Site Conditions** | | |
| Pyrexia | 2 (0.7) | 3 (1.0) |
| **Investigations** | | |
| Gamma-glutamyl transferase ↑ | 4 (1.3) | 4 (1.3) |
| ALT ↑ | -- | 3 (1.0) |
| AST ↑ | 1 (0.3) | 7 (2.3) |
| **Nervous System** | | |
| Headache | 4 (1.3) | 3 (1.0) |
| **Skin and Subcutaneous Tissue** | | |
| Rash | 3 (1.0) | 2 (0.7) |
| **Vascular System** | | |
| Phlebitis NOS | 2 (0.7) | 4 (1.3) |

*Treatment-related AEs include those that are of possible, probable, or unknown relationship to study treatment, as determined by the investigator.
† Maintenance dose

**SUMMARY AND RECOMMENDATION**
Anidulafungin should be approved for both of the following indications.

- Candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis). (see CLINICAL STUDIES and MICROBIOLOGY). ERAXIS has not been studied in endocarditis, osteomyelitis, and meningitis due to *Candida*, and has not been studied in sufficient numbers of neutropenic patients to determine efficacy in this group. [NDA 21-948]

- Esophageal candidiasis (see CLINICAL STUDIES, see Table 7 for higher relapse rates off anidulafungin therapy). [NDA 21-632]

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

/s/

Edward Cox
2/17/2006 04:11:09 PM
MEDICAL OFFICER

Renata Albrecht
2/17/2006 04:14:19 PM
MEDICAL OFFICER
NDA 21-632NDA 21-948

**Deputy Office Director and Division Director Review #2**

| | |
|---|---|
| **APPLICANT:** | **Pfizer/ Vicuron Pharmaceuticals, Inc.** |
| **DRUG:** | **Anidulafungin** |
| **TRADE NAME:** | **[ ] for Injection** |
| **NDA:** | **21-632** |
| **DATE OF SUBMISSION:** | **April 25, 2003** |
| **Major Amendment:** | **January 6, 2004** |
| **Approvable letter:** | **May 21, 2004** |
| **DATE OF RESUBMISSION:** | **May 27, 2005** |
| **PDUFA GOAL DATE:** | **November 27, 2005** |
| **FORMULATION:** | **Intravenous injection (50 mg)** |
| **INDICATION:** | **Esophageal candidiasis** |
| **RELATED MATERIAL:** | **Original Reviews: Drs Imo Ibia, Cheryl Dixon, Owen McMaster**<br>**Original Acting Office Director and Division Director Review**<br>**Approvable letter May 21, 2004**<br>**ODS Consult, Dr John Senior**<br>**Medical Review, Dr Elizabeth O'Shaughnessy**<br>**Statistical Review, Dr Cheryl Dixon**<br>**Microbiology Review, Lynn Steele Moore** |

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## A. RECOMMENDATIONS:

The applicant should be issued an approval letter, once final labeling discussions are complete. The deficiency identified in the May 21, 2004 approvable letter to Vicuron has been addressed. At the time of the action, final labeling has not been provided. Therefore an **Approvable letter** will be issued in response to the May 27, 2005 resubmission. The applicant will need to provide revised Final Printed Labeling (FPL) and revise the carton and container labels as is noted in the November 25, 2005 approvable letter.

## B. SUMMARY OF RESUBMISSION CONCLUSIONS

The deficiency in the May 21, 2004 letter identified concerns regarding risk-benefit and commented on the efficacy and safety findings in the esophageal candidiasis study.

NOTE: The applicant requested labeling regarding [ ] in the CLINICAL STUDIES section of the labeling. [ ]

[ ]

### 1) Deficiency

The text of the May 21, 2004 approvable letter is reproduced below in italicized font:

> *"A satisfactory risk-benefit ratio for the use of anidulafungin in the treatment of esophageal candidiasis has not been demonstrated. Clinical studies demonstrated a possible signal for hepatotoxicity, and the esophageal candidiasis study (VER002-4) demonstrated that anidulafungin has a higher relapse rate at the two-week post therapy visit than the comparator therapy. Even without the safety concern, the results of the single pivotal esophageal candidiasis study do not support the use of anidulafungin as initial therapy for esophageal candidiasis because of the high relapse rate at the two-week post therapy visit."*

A number of options were available to address the deficiency, and these are enumerated and answered below:

**2) Safety**
To address safety, specifically hepatic adverse events, the following guidance was provided (emphasis added)

> *"In order to address the concern regarding hepatic toxicity you must provide additional clinical data to further characterize the safety of anidulafungin. This information should be from clinical studies evaluating anidulafungin at doses and durations that equal or exceed the esophageal candidiasis regimen."*

To address the concern about hepatic toxicity, the company submitted additional data from approximately 300 subjects who received anidulafungin (this includes data from 131 anidulafungin-treated patients from Study VER002-9), an integrated safety analysis (145 pages), a Hepatic Safety Summary (781 pages) and a Hepatic Expert Report (101 pages). The latter analysis and report was provided by Dr. [ ] an expert hepatologist. The results of these analyses showed that there were some patients with elevations in liver function tests 2x, 3x, 5x and up to 10x the upper limit of normal, and possible hepatic adverse events in a background of underlying medical conditions and concomitant medications. These events were similar to that seen with other echinocandins, in terms of the underlying conditions in the patients. As a result of these findings, the following labeling is proposed for the first paragraph in the PRECAUTIONS section of the package insert. (See Section C. below.)

> PRECAUTIONS
> *Hepatic Effects*
> Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with [ ] In some patients with serious underlying medical conditions who were receiving multiple concomitant medications along with [ ] clinically significant hepatic abnormalities have occurred. Isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure have been reported in patients; a causal relationship to [ ] has not been established.
> Patients who develop abnormal liver function tests during [ ] therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing [ ] therapy

**3) Efficacy**
To address efficacy, especially anti-candidal activity, the following guidance was provided (emphasis added):

> *"In order to address the concern regarding the efficacy of anidulafungin, you must provide additional clinical data to address the observed high relapse rate and/or provide supportive evidence of anidulafungin's efficacy as an anti-candidal agent. This concern may be addressed by submitting results from one or both of the following types of studies:*
>
> - *An adequate and well- controlled study evaluating alternative regimens of anidulafungin to reduce the relapse rates in patients with esophageal candidiasis. This study would need to demonstrate both efficacy at the end of therapy and durability of response at the two-week follow-up visit to support the labeling of anidulafungin as initial therapy in esophageal candidiasis.*
>
> *AND/OR*
>
> - *An adequate and well- controlled study demonstrating the efficacy of anidulafungin in another infection due to Candida spp. This study would provide supportive evidence of anidulafungin's efficacy as an anti-candidal agent; however, it would*

> *not support labeling of anidulafungin as initial therapy in esophageal candidiasis because this type of study would not address the high relapse rate observed in study VER002-4."*

To provide corroborative information for anti-candidal activity, the applicant submitted results of study VER002-9, the comparative study of anidulafungin and fluconazole in candidemia and invasive candidiasis. The dosage regimen was 200 mg loading dose followed by daily doses of 100 mg IV, twice the daily amount of anidulafungin compared to recommended dosage regimen for the esophageal candidisis. The results of VER002-9 showed anidulafungin to be statistically superior to the comparative fluconazole regimen, therefore confirming the anti-candidal activity of anidulafungin (See Section D. below.)

**4) Approval**
The May 21, 2004 approvable letter commented on the criteria that would need to be met in order for anidulafungin to be approved, as stated below.

> *"In order to garner an indication for esophageal candidiasis, you will need to provide additional efficacy data as described above and also demonstrate an acceptable overall safety profile for anidulafungin, including the results of the additional clinical safety data submitted in response to this letter".*

The company addressed the hepatic toxicity question, demonstrated no new safety signal or adverse events that would preclude approval, and provided corroborative evidence of anti-candidal activity of anidulafungin. Therefore, with some revisions to the package insert and labeling, the application can be approved.

**5) Other indication**
Finally, the letter provided another option for the company to consider in seeking approval, namely developing anidulafungin for another indication, as stated below:

> *"Alternatively, you could develop and seek approval for anidulafungin for more serious antifungal infections (such as candidemia and invasive candidiasis) or for patients who have fewer therapeutic options (such as those with refractory Candida infections and/or intolerant of other products). A safety profile not acceptable in a less serious disease may be tolerated if efficacy is demonstrated in a more serious disease or for those with fewer therapeutic options."*

Consistent with PDUFA procedures, the applicant did not request approval of the candidemia and invasive candidiasis indication supported by VER002-9 as part of this resubmission action. Instead, the applicant has submitted a new drug application, NDA 21-948 on August 18, 2005 for this indication. Because of the finding of superiority in efficacy of anidulafungin vs fluoconazole based on the applicant's analysis, NDA 21-948 was given a priority review.

The original NDA and resubmission were submitted by Vicuron, Late in the review cycle, Pfizer assumed ownership or control of anidulafungin. Final labeling discussions will take place with Pfizer. Draft labeling was sent to Pfizer on November 18, and 23, 2005.

## C. SUMMARY OF SAFETY FINDINGS IN RESUBMISSION
**(excerpts from Dr. O'Shaughnessy's review and NDA 21-632)**

In the original NDA 21-632 submission, information from animal toxicology studies, Phase I studies at higher doses (260 mg loading /130mg maintainance) and particularly patient #13-008 who died with evidence of hepatotoxicity in the esophageal candidiasis study, VER002-4, raised the question of hepatotoxicity due to anidulafungin. Therefore, in the resubmission, the applicant provided a comprehensive review of safety on all patients enrolled in the anidulafungin clinical program, including an integrated summary of safety (145 pages), a Hepatic Safety Summary (781 pages) and a Hepatic Expert Report (101 pages).

**Integrated Summary of Safety**

In the resubmission, results of the following newly reported studies were included:

- VER002-7, Anidulafungin Plus AmBisome® [(Amphotericin B) Liposome for Injection] as a Treatment for Invasive Aspergillosis
- VER002-9, of Anidulafungin vs. Fluconazole in the Treatment of Patients with Candidemia and Other Forms of Invasive Candidiasis and Prevention of Complications, and extension VER002-9b (33 patients)
- VER002-11, Intravenous
- Anidulafungin as a Treatment for Azole-Refractory Mucosal CandidiasisVER002-12, Phase 1/2 Study of the Safety, Tolerance, and Pharmacokinetics of
- Anidulafungin in Immunocompromised Children with Neutropenia
- VER002-13, Pharmacokinetic Interaction Study Between VFEND(Voriconazole) and Anidulafungin
- VER002-15, Interaction Study Between Oral Tacrolimus (Prograf®, Fujisawa Healthcare, Inc.) and Intravenous Anidulafungin in Healthy Male Subjects

In the NDA and resubmission, 633 patients were exposed to daily doses of at least 50 mg of intravenous anidulafungin in Phase 2-3 studies; 319 had esophageal (or oropharyngeal) candidiasis, 284 had invasive candidiasis, and 30 had invasive aspergillosis. By daily dose, 359 patients received 50 mg/day, 40 patients received 75 mg/day, and 234 patients received 100 mg/day. (Table 1.1, upper portion of table). A total of 774 patients received anidulafungin when Phase 1 studies are included. A total of 426 fluconazole patients were enrolled.
A list of studies, patients enrolled, and drugs received is summarized in the table below, taken from applicant's ISS.

**Table 1.1 Studies Included in Amendment to Original NDA 21-632**

| Study Number | Phase | Original NDA? | Number of Subjects Exposed to Indicated Anidulafungin Dose (mg) 50 | 75 | 100 | Total Number of Subjects Exposed to Anidulafungin or Fluconazole Anid | Flu |
|---|---|---|---|---|---|---|---|
| Phase 2-3 Studies in Candidiasis or Aspergillosis | | | | | | | |
| Esophageal candidiasis | | | | | | | |
| VER002-4 | 3 | Yes | 300 | | | 300 | 301 |
| VER002-11 | 2 | Yes (Interim) | 19 | | | 19 | |
| Invasive candidiasis | | | | | | | |
| VER002-6 | 2 | Yes | 40 | 40 | 40 | 120 | |
| VER002-9 | 3 | No | | | 131 | 131 | 125 |
| VER002-9b[a] | 3 | No | | | 33 | 33 | |
| Aspergillosis | | | | | | | |
| VER002-7 | 2/3 | Yes (Interim) | | | 30 | 30 | |
| Phase 1 Special Population Studies | | | | | | | |
| Healthy subjects (PK/mass balance) | | | | | | | |
| VER002-1 | 1 | Yes | | 6[b] | 6 | 12 | |
| VER002-5 | 1 | Yes | | 10 | 20[c] | 30 | |
| VER002-10 | 1 | Yes | | | 9 | 9 | |
| Healthy subjects (drug interaction) | | | | | | | |
| VER002-8 | 1 | Yes | | | 12 | 12 | |
| VER002-13 | 1 | No | | | 18 | 18 | |
| VER002-15 | 1 | No | | | 35 | 35 | |
| Special population | | | | | | | |
| VER002-12 | 1/2 | No | 13[d] | | 12[e] | 25 | |
| Total | | | 372 | 56 | 346 | 774 | 426 |

Data source: VER002-4 CSR (Table 8), VER002-11 CSR (Table 6), VER002-6 CSR (Table 5.1), VER002-9 CSR (Table 39), VER002-9b (Table 1.5), VER002-7 CSR (Table 7), Item 8 of Original NDA 21-632 (ISS, Table 4.1), VER002-13 CSR (Table 14.1.1), VER002-15 CSR (Appendix 16.2.5.4.2), VER002-12 CSR (Table 13)
Anid = anidulafungin; Flu = fluconazole; PK = pharmacokinetics.
[a] Only interim safety data are provided. This study is not included among the 12 studies summarized.
[b] Subjects received 70-mg maintenance doses.
[c] Ten subjects received 100-mg doses, and 10 subjects received 130-mg maintenance doses.
[d] Received maintenance doses of 0.75 mg/kg/day, approximately 50-mg adult dose
[e] Received maintenance doses of 1.5 mg/kg/day, approximately 100-mg adult dose

After review of the clinical and laboratory information in the NDA and resubmission, a new safety signal or adverse events that would preclude approval of this application were not identified either in the applicant report or Medical Officer's review.

**Safety Summary VER002-9**

This was a phase 3 study in patients with candidemia and invasive candidiasis; patients received anidulafungin 200mg as a loading dose followed by 100 mg maintainance dose. A total of 256 patients were enrolled, 131 randomized to anidulafungin and 125 randomized to fluconazole.

Withdrawal from study medication was more frequent in the control arm. Withdrawal due to death occurred in 29 (22.1%) in the anidulafungin arm and 38 (30.4%) in the fluconazole arm before the 6 week follow up. In both the anidulafungin and fluconazole groups, cardiac arrest (2.9% anidulafungin, 5.6% fluconazole) was the most common AE resulting in death. There were no discernable patterns in the causes of death among anidulafungin-treated patients or between the anidulafungin and fluconazole treatment populations. A total of 12 patients (9.2%) on anidulafungin and 21 patients (16.8 %) on fluconazole withdrew for an adverse event. Withdrawal to worsening clinical condition/lack of efficacy was seen in 11 (8.4%) anidulafungin and 16 (12.8%) fluconazole patients.

No cases of anaphylaxis, or QT prolongation occurred. Hepatic adverse events were more common in the fluconazole arm of the study. No cases of hepatic failure occurred. There were 5 (3.8%) patients in the anidulafungin group and 8 (6.3%) patients in the fluconazole group who reported clinical adverse events categorized under the hepatobiliary category. Four of these events were severe in intensity and all four occurred in fluconazole-treated patients. One hepatic AE that was considered possibly related to study drug occurred in an anidulafungin-treated patient (ongoing cholestasis in a patient with disseminated candidiasis). However, this case was confounded because both disseminated candidiasis and concomitant medications could have caused the hepatic abnormalities that were observed.

The table below presents adverse events that were seen in ≥ 5% of the patients.

| **Adverse Events Experienced by ≥ 5% Patients in Either Study Arm, Study VER002-9** | | |
|---|---|---|
| | (ITT Population) | |
| | **Anidulafungin** | **Fluconazole** |
| | (N = 131) | (N = 125) |
| **Adverse Event** | n (%) | n (%) |
| Hypokalaemia | 33 (25.2) | 24 (19.2) |
| Nausea | 32 (24.4) | 15 (12.0) |
| Diarrhoea | 24 (18.3) | 23 (18.4) |
| Bacteraemia | 23 (17.6) | 23 (18.4) |
| Pyrexia | 23 (17.6) | 23 (18.4) |
| Vomiting | 23 (17.6) | 12 (9.6) |
| Insomnia | 20 (15.3) | 12 (9.6) |
| Urinary tract infection | 19 (14.5) | 22 (17.6) |
| Hypotension | 19 (14.5) | 18 (14.4) |
| Alkaline phosphatase increased | 15 (11.5) | 14 (11.2) |
| Hypomagnesaemia | 15 (11.5) | 14 (11.2) |
| Hypertension | 15 (11.5) | 5 (4.0) |
| Dyspnoea | 15 (11.5) | 4 (3.2) |
| Oedema peripheral | 14 (10.7) | 16 (12.8) |
| Pleural effusion | 13 (9.9) | 11 (8.8) |
| Deep vein thrombosis | 13 (9.9) | 9 (7.2) |
| Anaemia | 12 (9.2) | 20 (16.0) |
| Constipation | 11 (8.4) | 14 (11.2) |
| Headache | 11 (8.4) | 10 (8.0) |
| White blood cell count increased | 11 (8.4) | 3 (2.4) |
| Confusional state | 10 (7.6) | 10 (8.0) |
| Sepsis | 9 (6.9) | 11 (8.8) |
| Hypoglycaemia | 9 (6.9) | 10 (8.0) |
| Cough | 9 (6.9) | 7 (5.6) |
| Pneumonia | 8 (6.1) | 19 (15.2) |
| Abdominal pain | 8 (6.1) | 16 (12.8) |
| Hyperkalaemia | 8 (6.1) | 14 (11.2) |
| Hyperglycaemia | 8 (6.1) | 8 (6.4) |
| Depression | 8 (6.1) | 5 (4.0) |
| Dehydration | 8 (6.1) | 2 (1.6) |
| Respiratory distress | 8 (6.1) | 2 (1.6) |
| Thrombocythaemia | 8 (6.1) | 1 (0.8) |
| Hepatic enzyme increased | 7 (5.3) | 14 (11.2) |
| Back pain | 7 (5.3) | 13 (10.4) |
| Decubitus ulcer | 7 (5.3) | 10 (8.0) |
| Chest pain | 7 (5.3) | 6 (4.8) |
| Leukocytosis | 7 (5.3) | 6 (4.8) |
| Blood creatinine increased | 7 (5.3) | 1 (0.8) |
| Anxiety | 6 (4.6) | 13 (10.4) |

| | | |
|---|---|---|
| Rigors | 6 (4.6) | 11 (8.8) |
| Agitation | 6 (4.6) | 7 (5.6) |
| ALT increased | 6 (4.6) | 7 (5.6) |
| Staphylococcal bacteraemia | 6 (4.6) | 7 (5.6) |
| Cardiac arrest | 5 (3.8) | 11 (8.8) |
| Renal insufficiency | 5 (3.8) | 11 (8.8) |
| Renal failure acute | 5 (3.8) | 9 (7.2) |
| Hypothermia | 5 (3.8) | 8 (6.4) |
| Pulmonary oedema | 4 (3.1) | 13 (10.4) |
| Thrombocytopenia | 4 (3.1) | 13 (10.4) |
| Rash | 4 (3.1) | 11 (8.8) |
| Abdominal distension | 4 (3.1) | 8 (6.4) |
| Bradycardia | 3 (2.3) | 7 (5.6) |
| Dizziness | 3 (2.3) | 7 (5.6) |
| AST increased | 2 (1.5) | 9 (7.2) |
| Septic shock | 1 (0.8) | 10 (8.0) |
| Metabolic acidosis | 1 (0.8) | 7 (5.6) |
| Source: Data from Section 14.3, Table 3.7. | | |

*The reviewer noted that the anidulafungin treatment group had more GI symptoms such as nausea and vomiting compared to the fluconazole treatment group. Diarrhea was similar between the groups. Hepatic enzymes were elevated more often in the fluconazole arm. Metabolic acidosis, pulmonary edema, renal failure, renal insufficiency and pneumonia were more common in the fluconazole arm. Sepsis and bacteremia was balanced between the two arms but septic shock was more common in the fluconazole arm.*

**Hepatic Expert Report**

Dr [ ] Vicuron's hepatic consultant, presented his findings regarding hepatic adverse events. "At the request of Dr. [ ] all patients in Phase 3 studies were surveyed for increases in ALT, AST, alkaline phosphatase, or total bilirubin equal to or greater than twice the upper limit of normal." (p9[1]) The studies and numbers of patients that were evaluated are presented in the table below.

| **Number of Patients with Hepatic Figures and Narratives by Study*** | | | | | |
|---|---|---|---|---|---|
| **Study** | No. of anidulafungin/ fluconazole-treated patients | No. of hepatic figures for anidulafungin produced (patients with 2-fold increase in transaminases) | No. of narratives for anidulafungin requested by Dr. [ ] | No. of hepatic figures for fluconazole produced | No. of narratives for fluconazole requested by Dr. [ ] |
| VER002-4 | 300/301 | 102 | 2 | 103 | 2 |
| VER002-5 | 30 | 4 | 0 | NA | NA |
| VER002-6 | 120 | 70 | 4 | NA | NA |
| VER002-7 | 30 | 23 | 3 | NA | NA |
| VER002-9 | 131/125 | 78 | 1 | 49 | 6 |
| VER002-11 | 19 | 7 | 0 | NA | NA |
| VER002-12 | 25 | 8 | 0 | NA | NA |
| VER002-15 | 35 | 2 | 0 | NA | NA |
| **Total** | **690/426** | **294** | **10** | **152** | **8** |
| Source: Adapted from Hepatology Expert's Report, in submission 2005-05-27 | | | | | |

[1] Hepatic Safety Summary, NDA 21-632, page 9 of 78. The applicant states, "The objective of this document is to synthesize and analyze hepatic safety across all studies in the anidulafungin clinical development program that are applicable to the intended therapeutic usage. This will be prefaced by a brief overview of hepatic-related effects in the preclinical program, which provided a basis for the progression from preclinical to clinical evaluation."

*Compared to Table 1.1 from applicant's ISS, it is noted that studies 1, 9b, and 13 are not included in the Hepatology Expert Report. In the company's Hepatic Safety Expert Summary it states that liver events were examined in studies evaluating multiple doses applicable to the therapeutic range.

There were 294/690 (42.6%) anidulafungin patients and 152/426 (35.7%) who met the greater than 2 fold increase in hepatic enzymes and each subject had hepatic chemistry findings (AST, ALT, bilirubin, alkaline phosphatase) graphed and further reviewed to see if the hepatic chemistry fit the following conservative definition for Hy's Rule: ALT rise to > 2x ULN, and concomitant or up to one month delayed rise in bilirubin > 1.5x ULN. If the patient's baseline ALT or bilirubin was elevated, this baseline value replaced ULN in the search criteria. As shown in the above table, 10 anidulafungin and 8 fluoconazole patients were further evaluated by Dr. [redacted]

Dr [redacted] presents a good overview of changes seen during liver injury, his text is reproduced below:

"The most common form of clinically significant drug induced liver injury is hepatocellular injury. This is also the form of liver injury that is most relevant for anidulafungin, based on three observations just discussed. The most sensitive and specific biomarker for hepatocellular injury is serum alanine aminotransferase, or ALT. This protein is released from liver cells during hepatocellular injury; high elevations mean liver cells are dying, breaking open, and releasing their contents into the circulation. Aspartate aminotransferase, or AST, is also present in liver cells, but unlike ALT, is quite abundant in other tissues including blood cells and muscle. Marked serum AST elevations without comparable elevations in serum ALT are not suggestive of liver injury. For this reason, serum ALT is the primary biomarker used to detect hepatocellular injury in a safety database.

"A traditional approach to analyze ALT data is to determine treatment-related shifts in mean values. Another approach is to examine incidence of treatment related elevations or shifts in serum ALT above specified multiples of upper limits of normal (ULN), or multiples of the patient's baseline value if elevated. The group data obtained in this fashion can be compared to historical data from other drugs, or to the data obtained in comparator treatments in the same clinical trials. As outlined in the Sponsor's Hepatic Safety Summary in Tables 19 and 22, 27, 32, 36, aggregate analysis of peak serum ALT levels associated with anidulafungin treatment is quite reassuring. Most importantly, the incidence and height of serum ALT elevations observed in the clinical trials compares quite favorably to what was observed during comparator treatment (fluconazole) in trials VER002-4 and VER002-9. Clinically important liver injury from fluconazole has been reported, but this drug is generally considered to be relatively safe compared to at least several other antifungal agents (notably ketoconazole).

"It is also appreciated that aggregate data analysis has limitations. It has therefore become customary to search liver safety databases using certain biochemical criteria to identify, and then closely examine the treatment response in these patients.

"The most typical search parameter is combined elevations in serum ALT and bilirubin. This is based on observations by the late Hyman Zimmerman (or "Hy" to his friends), who noted that patients with hepatocellular injury due to a drug have a > 10% mortality rate once they become jaundiced. The presence of jaundice (bilirubin > 2.5 mg/dl) indicates that the usual great excess functional capacity of the liver has been destroyed due to an ongoing hepatocellular injury. This significant loss of global liver function indicates that the liver may be damaged beyond repair, even if the drug treatment is stopped. Based on this concept, it has been proposed that the most predictive liver safety "signal" is the elevation of both serum ALT and serum bilirubin. This concept has been termed "Hy's Rule"; cases in a liver safety database that satisfy Hy's Rule are termed "Hy's Rule cases". One caveat is that in all but the most fulminant of injuries, the rise in bilirubin should occur some time after the onset of the hepatocellular injury (i.e. elevation of serum ALT). A second caveat is that Hy's Rule does not apply to liver injuries that are largely cholestatic in nature. In this case, the liver's ability to process and excrete bilirubin is affected at the onset of the injury and bilirubin elevations do not reflect significant global dysfunction of the liver. A cholestatic component to the injury is indicated if there is a substantial elevation of serum alkaline phosphatase. Such cases would not satisfy Hy's Rule. A final and obvious caveat is that qualifying as a Hy's Rule case does not mean that the liver injury was the result of study drug. This can only be concluded after careful review of the clinical data.

"Based on the above considerations, safety databases are therefore routinely searched for patients who satisfy Hy's Rule. Various definitions of "Hy's Rule" cases exist, but the most conservative is elevation in serum bilirubin > 1.5 X ULN and serum ALT > 2 X ULN. If a patient's baseline serum bilirubin or ALT is elevated, this definition is commonly modified by replacing "ULN" with the baseline value. Setting the ALT cut off at 2 X ULN or baseline is very conservative because the serum ALT would typically be very high (>20 X ULN) during an acute hepatocellular injury sufficient to significantly impair the liver's ability to eliminate bilirubin.

**Table 2. Summary of Hy's Rule Cases and Causation Assessments:**

| **Anidulafungin Cases** | | **Fluconazole Cases** | |
|---|---|---|---|
| Patient Identification | Causation Assessments | Patient Identification | Causation Assessments |
| 13-008 | Probable shock liver | 17-002 | Not related* |
| 07-001 | Unlikely due to drug* | 18-003 | Due to TB drugs |
| 67-001 | Attributed to anidulafungin | 35-003 | "Benign post-operative cholestasis" likely |
| 41-006 | Unlikely due to drug* | 32-002 | Probable shock liver |
| | | 04-009 | Probable shock liver |
| | | 11-004 | Possibly related to fluconazole |
| | | 18-010 | Possibly related to fluconazole |
| | | 20-010 | Not related to fluconazole* |
| * Clear alternate etiologies not evident. | | | |

"A summary of the cases that fulfill the conservative Hy's Rule is shown in Table 2 above. The first observation is that there are more than twice as many Hy's Rule cases among patients receiving fluconazole compared to among patients receiving anidulafungin. This is the case even though the total number of patients receiving anidulafungin exceeds those taking fluconazole. As previously mentioned, fluconazole therapy has rarely been associated with clinically significant liver injury. However, fluconazole is considered among the least hepatotoxic of the systemic anti-fungal therapies. It is therefore unlikely that the Hy's Rule cases observed with this drug represent a true liver safety signal. Rather, I suspect these cases reflect liver injuries that can occur from multiple etiologies in desperately ill patients. It is tempting to speculate that the increased abundance of Hy's Rule cases among the fluconazole treated patients may reflect lower efficacy relative to anidulafungin.

"There is only one Hy's Rule case among the anidulafungin treated patients (67-001) that I feel must be considered the result of anidulafungin treatment. The gradual onset of this injury is reassuring, as it should allow recognition of the process while it is still reversible. It would seem reasonable to caution physicians to monitor for evidence of worsening hepatic function in patients who develop abnormal serum ALT during anidulafungin therapy.

Although Dr. [ ]' report identified 4 anidulafungin and 8 fluconazole patients that are reported to meet "Hy's rule," only 2 anidulafungin and 2 fluconazole patients were judged to have possible drug- related events as summarized in the excerpt from MO Table 44. The footnote to the table provides the text of Dr. [ ] summary regarding patient 033-001.

**Excerpt of Medical Officer Table 44, including only of cases considered related by one of the evaluators**

| | | | | | Causation Assessments and Comments | | |
|---|---|---|---|---|---|---|---|
| **ID #** | **Age Sex** | **Study Drug Exposure** | **Meds**** | **Comorbid Disease** | **Hepatologist** | **Investigator** | **FDA** |
| **Anidulafungin Cases** | | | | | | | |
| 033-001* | 56 M | 200/100mg X 28 days plus L-AmB | yes | Invasive Aspergillosis Acute leukemia | Related Not Hy's rule | Unrelated | Multifactorial Probably related |
| 067-001 | 33 F | 200/100mg X 30 d | yes | Pulmonary aspergillosis Tuberculosis | Related Hy's rule case | Unrelated | possibly related but confounded by TB drugs |
| **Fluconazole cases** | | | | | | | |
| 11-004 | 24 F | 800/400mg x 15 d | yes | Nasopharyngeal cancer Esophageal candidiasis | Not stated Hy's rule case | Possibly related | Possibly related |
| 18-010 | 74 M | 800/400mg x 15 d | yes | Bladder cancer | Not stated Hy's rule case | Possibly related | Possibly related |

*033-001: This is a 56 year old man who experienced an ~ 8-fold elevation in serum ALT and a 2.5-fold elevation in serum bilirubin throughout the second half of a 28 day treatment with anidulafungin. This patient's serum alkaline phosphatase also rose almost 5-fold during this period, indicating a large cholestatic component to the liver injury. This is therefore **not a Hy's Rule case.** There was a prompt dechallenge, **consistent with drug toxicity**.
****Prior and concomitant meds with potential for liver toxicity**
Note: L-AmB=Liposomal Amphotericin

Case 67-001 was reviewed by FDA's hepatology consultant who had a different interpretation of this patient's findings. In ODS consultation #D050601, he writes,

> "33-year-old black woman who was admitted to a hospital in South Africa on [ ] for treatment of hemoptysis thought to be due to reactivation of tuberculosis based on a radiology report. She was treated on a regimen of ethambutol, isoniazid, pyrazinamide, and rifampicin from [ ] but her smears for acid-fast bacilli and tuberculosis were negative. Bronchoscopy on [ ] disclosed that aspirates showed Aspergillus fumigatus and she was treated with IV anidulafungin and liposomal amphotericin B from [ ]
> *The case for anidulafungin-induced acute hepatocellular injury is weak, and it is somewhat more likely an isoniazid-pyrazinamide-induced injury, although not for certain. Like so many of the cases of drug-induced liver injury, there were too many possible causes, and none can be implicated with any high degree of likelihood."*

Also noted in Dr. [ ]' review is patient #13-008 from VER002-4 whose death with evidence of hepatotoxicity raised concerns about possible drug toxicity. However on further review by the hepatologist, the patient's death was attributed to shock liver as a result of congestive heart failure.

On the other hand, when only patients from the comparative studies VER00-4 (EC) and VER002-9 (candidemia/IC) were evaluated, the following values were seen: 4/283 (1.4%) anidulafungin and 2/277 (0.7%) fluconazole patients met a somewhat different definition of Hy's Rule with ALT > 3x ULN and bilirubin > 1.5x ULN. While ALT elevations are numerically higher in the fluconazole arm, the AST elevations are numerically higher in the anidulafungin arm (See table below). Upon review of the cases, the Medical Officer concluded that none were judged to be drug-related.

**Integrated Summary of Hepatobiliary Parameters from Comparative Phase 3 Data On-Therapy**

| Hepatic parameter | Anidulafungin | Fluconazole |
|---|---|---|
| ALT> X3 ULN | 18/376 (4.8%) | 27/364 (7.4%) |
| ALT > X5 ULN | 6/376 (1.6%) | 9/364 (2.5%) |
| ALT > 10 ULN | 0/376 (0.0%) | 1/364 (0.27%) |
| AST > X3 ULN | 43/374 (11.5%) | 39/364 (10.7%) |
| AST > X5 ULN | 17/374 (4.5%) | 14/364 (3.8%) |
| ALT > X3 ULN and bilirubin > X1.5 ULN | 4/283 (1.41%) | 2/277 (0.72%) |

In reading the case summaries for patients with reported hepatic findings, it was noted that these patients had various underlying medical conditions and concomitant medications that could have accounted for/contributed to the hepatic findings and confounded the interpretation of the findings, just as was noted in Dr. [ ]' and Dr. Senior's consultative reports.

**Hepatic Safety Summary**

The applicant writes,

> "Overall, 24 clinical studies comprise the clinical development program for anidulafungin. All of these studies with the exception of the on-going open-label extension of Study VER002-9 (VER002-9b) have been summarized relative to hepatic safety in this review. The summary of safety in this NDA amendment concentrates on the overall safety of 12 of these studies involving 50 mg/day (the recommended dose for the indication of esophageal candidiasis) and 100 mg/day intravenous maintenance doses for invasive fungal infections (Table 38). Eight of these studies were included in the original NDA (provided in Item 8 of original NDA 21-632). Four are new studies conducted after the original submission and two studies had only interim data presented in the original NDA. The remaining studies were fully discussed in Item 8 of the original NDA; five of these studies were oral formulation studies, three were Phase 1 studies in healthy volunteers, two were studies in special populations, and two were Phase 2 studies of intravenous anidulafungin at maintenance dosages of 35 and 25 mg/day in subjects with esophageal candidiasis or invasive candidiasis including candidemia.
>
> "Across the clinical development program, the majority of hepatobiliary laboratory findings either did not meet absolute value criteria for potential clinical significance or were not potentially clinically significant changes from baseline. "

**Conclusion:**

The detailed evaluation of hepatic adverse events by the applicant and their consultant as well as by FDA shows that there were hepatic events documented during the study, including patients who died and had derangement in hepatic laboratory tests and evidence of hepatitis. However, in essentially all of these patients, there was evidence of underlying medical conditions and/or the use of concomitant medications that either was responsible for the hepatic findings or where anidulafungin or fluconazole were not considered causative but an association with the use of the drug could not be excluded. Given these findings, and specifically the absence of any unconfounded cases where the study drug was the sole potential etiology for hepatic toxicity, the labeling for anidulafungin should carry the following information as the first paragraph in the PRECAUTIONS section of the labeling:

> PRECAUTIONS
> *Hepatic Effects*
> Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with [ ]. In some patients with serious underlying medical conditions who were receiving multiple concomitant medications along with [ ], clinically significant hepatic abnormalities have occurred. Isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure have been reported in patients; a causal relationship to [ ] has not been established.

Patients who develop abnormal liver function tests during [ ] therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing [ ] therapy.

**D. SUMMARY OF EFFICACY FINDINGS IN RESUBMISSION**
**(excerpts from Dr. O'Shaughnessy's review)**

Results of a phase 3, double-blind (third-party unblinded) randomized, multi-center, comparative study, VER002-9, were submitted. In this study 256 patients constituted the ITT population; 131 received 100 mg IV anidulafungin, and 125 received 400 mg IV fluconazole for 14 to 42 days. Candidemia was present in more than 90% of patients in both study arms. Approximately half of all patients had invasive candidiasis related to an IV catheter (per investigator attribution). Most patients had a single baseline pathogen; *Candida albicans* was isolated in the majority of patients. The number of treated patients by country was USA (185), Canada (59), Belgium (2), Germany (3) and Italy (6) and Netherlands (1). The largest number of patients (25) were enrolled at a single site in Canada.

The primary objective was to determine if anidulafungin is at least as effective as fluconazole with respect to the global response (combined clinical and microbiological response at the end of IV therapy) for the treatment of patients with a diagnosis of candidemia and/or other forms of invasive candidiasis.

All patients were to receive the study medication for minimum treatment duration of 14 days from the time of the last negative culture and improvement of clinical signs and symptoms of candidemia or invasive candidiasis. Total treatment duration was not to exceed 42 days. Patients in either group were permitted to switch to oral fluconazole (400 mg/daily) after at least 10 days of IV treatment if the following criteria were met:

- the patient was afebrile for at least 24 hours;
- the patient was able to tolerate oral medications;
- the last blood culture was negative for *Candida* species;
- reduction of signs and symptoms of the *Candida* infection such that the Investigator felt it was appropriate to switch to oral fluconazole (oral fluconazole was not to be given as prophylaxis).

The patients were followed for safety through the 6-week follow-up (FU) visit.

The results for the primary endpoint, Global Response at End of IV Therapy, the results for additional analyses at secondary time points, and by pathogen response are summarized in the tables that follow. (Note: the proposed indication for invasive candidiasis / candidemia is the subject of NDA 21-948, which is currently under review.)

| **Response at End of IV Therapy (Micro-ITT Population) – primary endpoint, VER002-9** | | | | |
|---|---|---|---|---|
| | **Anidulafungin** | **Fluconazole** | | |
| **Response** | (N = 127) | (N = 118) | Between-Group | |
| Outcome | n (%) | n (%) | Difference[a] | (95% CI) |
| **Success** | 96 (75.6) | 71 (60.2) | 15.42% | (3.85 , 26.99) |
| **Failure** | 31 (24.4) | 47 (39.8) | | |
| a: Anidulafungin minus fluconazole. | | | | |
| Source: Data from Section 14.2, Table 2.1.1. | | | | |

| **Global Response at End of IV Therapy and Secondary Time Points in the Micro-ITT Population, VER002-9** | | | |
|---|---|---|---|
| **Time point** | **Anidulafungin** | **Fluoconazole** | **Between-Group Difference (95%CI)** |
| End of IV Therapy | 96/127 (75.6) | 71/118 (60.2) | 15.4% (3.85 , 26.99) |
| End of Oral Therapy | 31/33 (93.9) | 28/33 (84.8) | 9.1% (-5.60 , 23.79) |
| End of All Therapy | 94/127 (74.0) | 67/118 (56.8) | 17.2% (5.49 , 28.99) |
| 2-Week Follow-Up | 82/127 (64.6) | 58/118 (49.2) | 15.4% (3.14 , 27.68) |
| 6-Week Follow-Up | 71/127 (55.9) | 52/118 (44.1) | 11.8% (-0.60 , 24.28) |

| Global Success at End of IV Therapy by Pathogen (Micro-ITT Population), VER002-9 | | |
|---|---|---|
| | **Anidulafungin** | **Fluconazole** |
| **Baseline Species** | n/N (%) | n/N (%) |
| All species | 92/119 (77.3) | 65/106 (61.3) |
| *Candida albicans* | 60/74 (81.1) | 38/61 (62.3) |
| Non-*albicans* species | 32/45 (71.1) | 27/45 (60.0) |
| *Candida glabrata* | 9/16 (56.3) | 11/22 (50.0) |
| *Candida tropicalis* | 13/14 (92.9) | 4/8 (50.0) |
| *Candida parapsilosis* | 7/11 (63.6) | 10/12 (83.3) |
| *Candida guilliermondii* | 2/2 (100.0) | -- |
| *Candida krusei* | 0/1 (0.0) | -- |
| *Candida lusitaniae* | 1/1 (100.0) | 1/2 (50.0) |
| *Candida famata* | -- | 1/1 (100.0) |
| Note: N=Number of patients with a single baseline pathogen.<br>Source: Data from Section 14.2, Table 2.12. | | |

**E: SUMMARY AND RECOMMENDATION**

The applicant has addressed the deficiency in the May 21, 2004 approvable letter for NDA 21-632. The application can be approved pending completion of the labeling discussions and provision of revised Final Printed Labeling (FPL) and revised carton and container labels. Pfizer recently acquired Vicuron (and anidulafungin) and indicated they are not likely to negotiate the labeling at this time.

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/s/
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Edward Cox
11/25/2005 01:48:04 PM
MEDICAL OFFICER

Renata Albrecht
11/25/2005 02:23:27 PM
MEDICAL OFFICER

**Memorandum**

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

DATE: 1 November 2005

FROM: John R. Senior, M.D., Associate Director for Science, Office of Pharmaco-epidemiology and Statistical Science (OPSS), HFD-030

TO: Renata Albrecht, M.D., Director, Division of Special Pathogen and Immunologic Drug Products (DSPIDP), HFD-590
Elizabeth O'Shaughnessy, M.D., Medical Reviewer, HFD-590

VIA: Mark Avigan, M.D., Director, Division of Drug Risk Evaluation, HFD-400, Office of Drug Safety (ODS)
Paul Seligman, M.D., Director, (OPSS), HFD-030

SUBJECT: ODS consultation #D050601 regarding hepatotoxicity possibly induced by use of anidulafungin for treatment of invasive bronchopulmonary Aspergillus infection

Documents reviewed:
1) Consultation request from HFD-590 dated 27 October 2005, assigned #D050601 on 31 October
2) E-mail request dated 27 October 2005 from Dr. Elizabeth O'Shaughnessy, and clinical study report VER002-7 from the sponsor concerning patient V2-7-67-001
3) Medical literature (PubMed) on antifungal toxicity
4) DFS listings for reviews submitted up to 31 October 2005 for anidulafungin, N 021632 and N 021-948
6) My consultation report of 24 March 2004 to HFD-590 on anidulafungin hepatotoxicity

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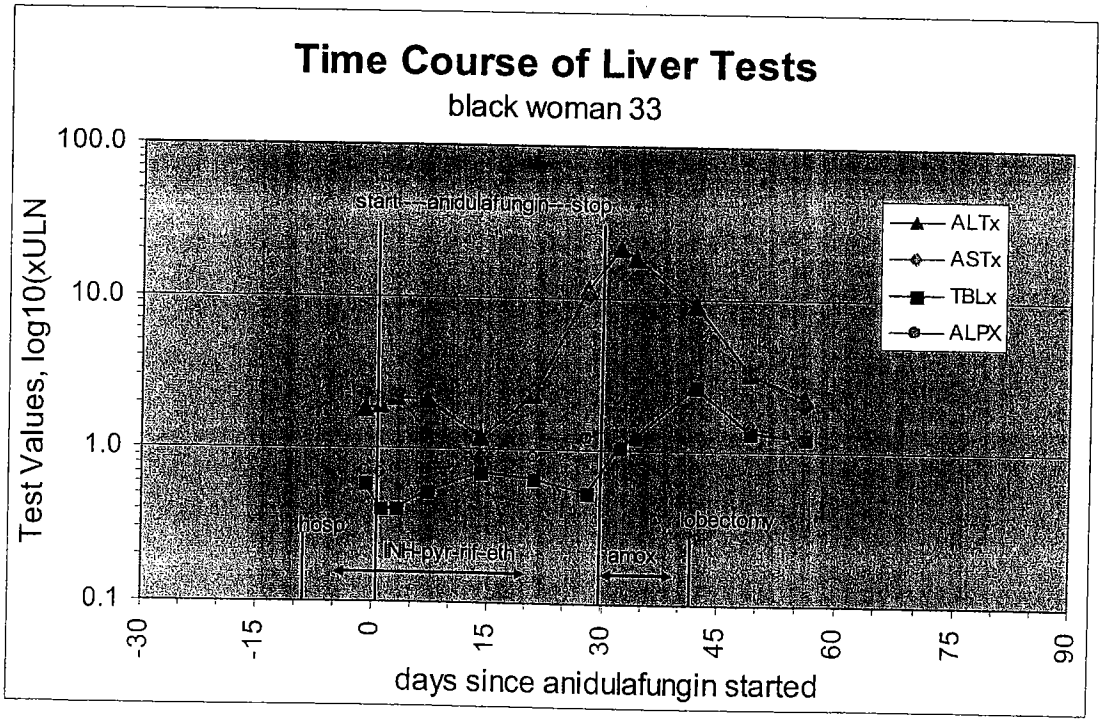
Dr. O'Shaughnessy asked on 27 October 2005 that we review and evaluate a case of non-fatal but serious liver injury occurring in a patient who had received 30 days of intravenous anidulafungin and AmBisome for treating an invasive Aspergillus infection. The patient was a 33-year-old black woman who was admitted to a hospital in South Africa on [ ] for treatment of hemoptysis thought to be due to reactivation of tuberculosis based on a radiology report. She was treated on a regimen of ethambutol, isoniazid, pyrazinamide, and rifampicin from [ ] but her smears for acid-fast bacilli and tuberculosis were negative. Bronchoscopy on [ ] disclosed that aspirates showed Aspergillus fumigatus and she was treated with IV anidulafungin and liposomal amphotericin B from [ ]

The patient had a history of chronic obstructive airway disease for which she had been treated with steroids and was said to have consequent acquired immunodeficiency, pulmonary tuberculosis of the left lung (1990), with asthma, dyspnea, hemoptysis, as well as recurrent urinary tract infections, painful legs , all before the diagnosis of pulmonary aspergillosis was made. She was not overweight (height 158 cm, weight 53 kg); date of birth [ ]

Monitoring of serum alanine and aspartate aminotransferase (ALT and AST) activities and alkaline phosphatase (ALP) activity and total bilirubin (TBL) concentration was started [ ] the day of bronchoscopy . She showed slight elevations of AST and ALT, in the range of 2 times the upper limit of the normal range (xULN) until [ ] but sharp increases in late [ ] peaking on [ ] The anti-tuberculosis regimen was stopped on [ ] and the anidulafungin-AmBisome treatment was stopped on [ ] The abnormal serum enzyme values continued to increase after the medications were stopped, and the ALP became slightly elevated. Peak values for ALT, AST, and ALP were noted on [ ] and the TBL peaked at 2. 65 xULN on [ ] after which all the abnormalities began to subside, and fell toward near-normal by [ ] the last reported follow-up information . Symptoms of generalized body pain were reported from [ ] [ ] a transient skin rash of the forearm on [ ] only, laboratory values indicating hypokalemia, hypomagnesemia, and neutropenia (no numbers provided) from [ ] to [ ]. The investigator expressed uncertainty as to which drugs may have caused the liver test abnormalities, but a consulting hepatologist attributed the liver injury to anidulafungin ( and said the investigator considered the event probably related to anidulafungin).

*Comment: This case description as provided by the sponsor ;eaves several questions unanswered, including why her AST and ALT were modestly elevated in late [ ] There is no mention of whether or not she may have been an alcohol user, which could have explained the findings seen. There is no report of attempts to exclude disease causes for the sharp rise in serum ALT, and AST in late [ ] including hepatitis A, B, and other viral infections, autoimmune or ischemic liver injury, etc. There may be more information available that was not provided with this report, which presumes the acute liver injury was drug-induced hepatocellular injury. It may have been, but it would be useful to know more. Let us look carefully at a graphic display of the course:*



*If what was observed was indeed drug-induced, then which drug or drugs caused it? The most likely culprits were the isoniazid-pyrazinamide regimen that are well known to cause liver injury. It seems considerably less likely to me that the anidulafungin treatment caused the injury, although it is still possible. The delay of a week or 10 days since the antituberculosis regimen was stopped is well within the range of latency for those drugs, and the delay cannot be taken to rule them out as a cause. The worsening of the hepatocellular injury after all drugs were stopped is also a well known phenomenon, and improvement often takes some weeks after offending drugs are stopped. It may be noted that the bilirubin peaked at 2.65 xULN two weeks after the anidulafungin was stopped, and over three weeks after isoniazid was stopped, again not unusual for drug-induced liver injury. I agree that this is a "Hy's Law" case, which means it was potentially serious, but hospitalization was for work-up of her hemoptysis and not because she was sick with acute liver failure. Alternative causes include trimethoprim-sulfamethoxazole (which usually causes cholestatic injury, not seen here), fluconazole (only three days) and acetaminophen, but amounts are not given. She also was treated with amoxicillin for 9 days starting in [ ] after the hepatic injury had occurred.*

*The case for anidulafungin-induced acute hepatocellular injury is weak, and it is somewhat more likely an isoniazid-pyrazinamide-induced injury, although not for certain. Like so many of the cases of drug-induced liver injury, there were too many possible causes, and none can be implicated with any high degree of likelihood. Why has it taken over three years for this case to be reported? The literature reports no anidulafungin-induced hepatotoxicity. There is no absolute or "gold" standard for determining causality of drug-induced liver injury; we are stuck with opinions, and in this case mine differs from that of their consultant (Dr. [ ] whom I know very well.*

Recommendations:

1. This case does not provide convincing evidence for anidulafungin-induced hepatocellular injury, which remains a distant possibility but appears somewhat less likely than isoniazid-pyrazinamide-induced liver injury, a well known phenomenon. A combination drug effect cannot be excluded.

2. The trail is old and cold, with over 3 years since the acute events occurred, but perhaps the sponsor could provide additional information as to her current status, past use of alcohol, and whether she has had further treatment for her pulmonary aspergillosis, and if so, what. Your note said you have requested more clinical information; let me know if you get it.

John R. Senior, M.D.

cc: ODS PID#D050601
M. Avigan, ODS/DDRE
P. Seligman, OPSS
S. Birdsong, DDRE
R. Albrecht, HFD-590
E. O'Shaughnessy HFD-590
L Sacks, HFD-590
D. Duggan, HFD-590

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/s/
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John Senior
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MEDICAL OFFICER
linked to original NDA submission of 25 Apr 2003

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PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# REQUEST FOR CONSULTATION

TO *(Division/Office)*:
**Director, Division of Medication Errors and Technical Support (DMETS), HFD-420**
**WO22, RM 4447**

FROM: Don Duggan
Division of Special Pathogen and Transplant Products

| DATE | IND NO. | NDA NO. | TYPE OF DOCUMENT | DATE OF DOCUMENT |
|---|---|---|---|---|
| 10/25/2005 | | 21-632 | | |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| [redacted] | | 7030410 | November 18, 2005 |

NAME OF FIRM: Vicuron Pharmaceuticals Inc.

**REASON FOR REQUEST**

**I. GENERAL**

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

**II. BIOMETRICS**

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| ☐ TYPE A OR B NDA REVIEW<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>OTHER (SPECIFY BELOW): | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ OTHER (SPECIFY BELOW): |

**III. BIOPHARMACEUTICS**

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

**IV. DRUG EXPERIENCE**

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

**V. SCIENTIFIC INVESTIGATIONS**

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: DMETS reviewed the proposed drug name [redacted] and filed a review in DFS on November 4, 2003. No issues with the proposed trade name were identified at that time. The PDUFA Goal Date for NDA 21-632 is November 27, 2005. The Division plans to take an action on November 18, 2005.

**PDUFA DATE: 11/27/2005**
**ATTACHMENTS:** Draft Package Insert, Container and Carton Labels
**CC:** Archival IND/NDA
HFD- /Division File
HFD- /RPM
HFD- /Reviewers and Team Leaders

| NAME AND PHONE NUMBER OF REQUESTER | METHOD OF DELIVERY (Check one) |
|---|---|
| Don Duggan/301-796-0584 | ☒ DFS ONLY ☐ MAIL ☐ HAND |
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

5/28/05

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/s/

Diana Willard
10/25/2005 07:31:19 PM
Diana Willard for Donovan Duggan III/NDA 21-632 Consult Request for Proposed Tradename

19 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

# Teleconference Minutes

**Telecon Date:** July 18, 2005

**Application #:** NDA 21-632: L J (anidulafungin)

**Sponsor:** Vicuron Pharmaceuticals

**Attendees:**

**Vicuron Pharmaceuticals**

| | |
|---|---|
| Eve Damiano | VP Regulatory Affairs |
| Beth Goldstein | Director of Microbiology |
| David Krause | Executive VP and Chief Medical Officer |
| Marty Stogniew | Executive VP, Scientific Affairs |
| Michele Wible | Director, Biostatistics |

**FDA- Division of Special Pathogen and Immunologic Drug Products**

| | |
|---|---|
| Shukal Bala, Ph.D. | Microbiology Team Leader |
| Lynn Steele-Moore | Microbiology Reviewer |
| Leonard Sacks, M.D. | Medical Team Leader |
| Elizabeth O'Shaughnessy, M.D. | Medical Reviewer |
| Kristen Miller, Pharm.D. | Regulatory Project Manager |

**Background**

On May 27, 2005, Vicuron Pharmaceuticals submitted a complete response to NDA 21-632. On July 1, 2005, Vicuron was sent microbiology comments pertaining to the presentation of data in the May 27, 2005 submission. Vicuron requested a telecon to receive clarification on these requests.

**Discussion Points**

Vicuron requested clarification of comment 1, "Please provide a summary Table of the results from study VER002-4 (and all other studies) by baseline pathogen for the per protocol set in the two treatment arms as shown in Table 1 labeled "Clinical and mycological response by pathogen". Patients with a single baseline pathogen (C. albicans, C. glabrata, etc) and those patients with mixed infection (C.albicans + C. tropicalis, C. albicans + C. glabrata, etc) should be shown separately", from the July 1, 2005 request. The Division clarified that only information that has not been previously submitted should be included in the format provided. Vicuron noted that the only new data contained in the resubmission were from Study VER002-9, entitled "A Phase III, Double-Blind, Randomized, Multi-center, Study of the Safety and Efficacy of Anidulafungin Vs. Fluconazole in the Treatment of Patients with Candidemia and Other Forms of Invasive Candidiasis and Prevention of Complications", and 19 patients from Study VER002-11, entitled "A phase II

Open-label Study of the Safety and Efficacy of Intravenous Anidulafungin as a Treatment for Fluconazole-Refractory Mucosal Candidiasis." The Review Team requested that the per protocol data from Studies VER002-9 and VER002-11 be provided in a format similar to Table 2 from the July 1, 2005 request, with mixed infections separated out and super-infections included. Additionally, the variables for clinical and micro outcome should correlate with the timepoints of baseline, end of treatment and follow-up. Vicuron agreed and suggested that they design a dataset and send it to the Division for comment. The Review Team concurred with this plan.

Vicuron noted that various methodologies for MIC testing were used within and across studies, and have evolved over time and proposed to utilize the methodology presented in-text in each study report. The Review Team agreed that this was acceptable provided that the methodology used is noted on the table as well. Vicuron is unclear what the Review Team was referring to in Comment 2 of the July 1, 2005 request where it stated "please define Global Response as stated on JMP table anidAMRPTL." Both Vicuron and the Review Team will refer to table anidAMRPTL to determine if global response was recorded. Vicuron stated that a proposed table design containing only new information (data from Studies VER002-9 and VER002-11) will be submitted by the end of the week and the telecon was adjourned.

**Action Items:**

1. Vicuron will submit a proposed table design by July 22, 2005. The table will include:
    a. Only per protocol data that has not been previously submitted (data from Studies VER002-9 and VER002-11)
    b. Mixed infections will be separated out and super-infections included
    c. Variables for clinical and micro outcome will correlate with baseline, end of treatment and follow-up.
2. Vicuron will utilize the methodology presented in-text in each study report, and note the methodology used on the table

Minutes Preparer: Kristen Miller, Pharm.D.; Project Manager
Concur: Shukal Bala, Ph.D.; Microbiology Team Leader

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/s/

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Kristen Miller
7/25/05 02:59:44 PM
CSO

Shukal Bala
7/25/05 03:11:38 PM
MICROBIOLOGIST

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation IV**

# FACSIMILE TRANSMITTAL SHEET

**DATE: July 1, 2005**

| | |
|---|---|
| **To:** Drew Sansone | **From:** Kristen Miller, Pharm.D. |
| **Company:** Vicuron | Division of Special Pathogen and Immunologic Drug Products |
| **Fax Number:** 610-490-2298 | **Fax Number:** 301-827-2475 |
| **Phone Number:** 610-490-2218 | **Phone Number:** 301-827-2127 |

**Subject:** Requests from Micro reviewer on resubmission

**Total no. of pages including cover:** 5

**Comments:**

**Document to be mailed:** YES ☑ NO

Please refer to your May 27, 2005 resubmission to NDA 21-632 (anidulafungin). The microbiology reviewer has the following requests for information:

1. Please provide a summary Table of the results from study VER002-4 (and all other studies) by baseline pathogen for the per protocol set in the two treatment arms as shown in Table 1 labeled "Clinical and mycological response by pathogen". Patients with a single baseline pathogen (*C. albicans, C. glabrata,* etc) and those patients with mixed infection (*C.albicans* + *C. tropicalis*, *C. albicans* + *C. glabrata,* etc) should be shown separately.

2. Please provide a Sas Transport File for Study VER002-4 (and all other studies) which includes the patient ID, treatment group, organism by species, culture source, phase isolated, MIC data, microbiology and clinical outcomes at EOT and FU as shown in Table 2. Please define Global response as stated on JMP table anidAMRPTL.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-827-2127 if you have any questions regarding the contents of this transmission.

_____

Kristen Miller, Pharm.D.
Regulatory Project Manager

Table 1: Clinical and mycological response by pathogen in the microbiologically evaluable per protocol set

| Treatment Group | End of Therapy : Defined as 14 – 21 days of treatment n /N (%) | | | | Follow-Up: Defined as 14 days post treatment n /N (%) | | | |
|---|---|---|---|---|---|---|---|---|
| | Clinical Success | Proven Mycologic Eradication | Presumed Mycologic Eradication | Global Response | Clinical Success | Proven Mycologic Eradication | Presumed Mycologic Eradication | Global Response |
| **Anidulafungin** | | | | | | | | |
| *C. albicans* | | | | | | | | |
| *C. tropicalis* | | | | | | | | |
| *C. krusei* | | | | | | | | |
| *C. glabrata* | | | | | | | | |
| *C. parapsilosis* | | | | | | | | |
| *Candida spp.* | | | | | | | | |
| *C. albicans + C. glabrata* | | | | | | | | |
| *C. albicans + C. krusei* | | | | | | | | |
| *C. albicans + C. tropicalis* | | | | | | | | |
| **Total** | | | | | | | | |
| **Fluconazole** | | | | | | | | |
| *C. albicans* | | | | | | | | |
| *C. tropicalis* | | | | | | | | |
| *C. krusei* | | | | | | | | |
| *C. glabrata* | | | | | | | | |
| *C. parapsilosis* | | | | | | | | |
| *Candida spp.* | | | | | | | | |
| *C. albicans + C. glabrata* | | | | | | | | |
| *C. albicans + C. krusei* | | | | | | | | |
| *C. albicans + C. tropicalis* | | | | | | | | |
| **Total** | | | | | | | | |

Table 2: Clinical microbiology dataset sample template for clinically evaluable, MITT per protocol set (Study VER0024):

| PtID | Treatment group | Organism (Species) | Culture source | phase | MIC (µg/mL) | | Micro Outcome ** | Clinical outcome *** |
|---|---|---|---|---|---|---|---|---|
| | | | | | Anid | Flucon | | |
| 1001 | Anid | *C. albicans* | Biopsy EC | Baseline | 0.03 | 0.5 | Success | Success |
| 1001 | Anid | *C. glabrata* | Throat OPC | End of treatment (EOT) | 0.03 | 0.5 | Success | Success |
| 1001 | Anid | - | - | Post-treatment (FU) | - | - | Success | Success |
| 1002 | Anid | *C. albicans* | Blood | Post-treatment | 0.03 | 0.5 | Success | Success |
| 2004* | Anid | *C. tropicalis* | Biopsy EC | Baseline | 0.03 | 0.5 | Success | Success |
| 2004* | Anid | *C. krusei* | Blood | Baseline | 0.03 | 0.5 | Failure | Failure |
| 4001 | Flucon | *C. tropicalis* | Biopsy EC | Baseline | 0.03 | 0.5 | Success | Success |
| 4002 | Flucon | *C. krusei* | Biopsy EC | Baseline | 0.03 | 0.5 | Success | Success |
| 4007 | Anid | *C. lipolytica* | Biopsy EC | Post-treatment | 0.03 | 0.5 | New infection | Success |
| 5003 | Anid | *C. tropicalis* | OPC | Baseline | 0.03 | 0.5 | Success | Success |
| 5003 | Anid | *C. tropicalis* | OPC | Post-treatment | 0.03 | 0.5 | Failure | Failure |

*Underline patients with mixed infections at baseline, irrespective of culture source

** Success includes: Proven eradication, presumed eradication, colonization Failure includes: Proven persistence, presumed persistence, proven recurrence, presumed recurrence, superinfection

***Success includes: Cure and improvement. Failure includes: Failure and indeterminate

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/s/

Kristen Miller
7/1/05 02:57:11 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

4/21/05

NDA 21-632

Vicuron Pharmaceuticals Inc.
Attention: Mr. Drew Sansone
Associate Director, Regulatory Affairs
355 South Gulph Road, Suite 310
King of Prussia, PA 19406

Dear Mr. Sansone:

Please refer to the meeting between representatives of your firm and the FDA on March 21, 2005. The purpose of the meeting was to discuss the resubmission plans of NDA 21-632 for anidulafungin and future submission plans for a new drug application for the indication of invasive candidiasis.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kristen Miller, Pharm.D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

*{See appended electronic signature page}*

Mark Goldberger, M.D., M.P.H
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

# MEMORANDUM OF MEETING MINUTES

| | |
|---|---|
| **MEETING DATE:** | March 21, 2005 |
| **TIME:** | 11:00 AM |
| **LOCATION:** | U.S. Food and Drug Administration<br>Center for Drug Evaluation and Research<br>Division of Special Pathogen and Immunologic Drug Products<br>9201 Corporate Blvd., S400<br>Rockville, MD 20850 |
| **APPLICATION:** | NDA 21-632 (Anidulafungin) |
| **TYPE OF MEETING:** | Pre-NDA Resubmission Meeting |
| **MEETING CHAIR:** | Mark Goldberger, M.D., M.P.H; Director, Office of Drug Evaluation IV (ODEIV) |
| **MEETING RECORDER:** | Kristen Miller, Pharm.D.; Regulatory Project Manager |

**FDA Attendees:**

| | |
|---|---|
| Mark Goldberger, M.D., M.P.H. | Director, ODEIV |
| Edward Cox, M.D., M.P.H. | Deputy Director, ODEIV |
| Renata Albrecht, M.D. | Director, Division of Special Pathogen and Immunologic Drug Products (DSPIDP) |
| Steven Gitterman, M.D., Ph.D. | Deputy Director, DSPIDP |
| Marc Cavaillé-Coll, MD, Ph.D. | Medical Officer Team Leader |
| Leonard Sacks, M.D. | Medical Officer Team Leader |
| Elizabeth O'Shaughnessy, M.D. | Clinical Reviewer |
| Cheryl Dixon, Ph.D. | Statistics Reviewer and Acting Team Leader |
| Philip Colangelo, Pharm.D., Ph.D. | Clinical Pharmacology/Biopharmaceutics Team Leader |
| Owen McMaster, Ph.D. | Pharmacology Toxicology Reviewer |
| Lynn Steele-Moore | Microbiology Reviewer |
| Shukal Bala, Ph.D. | Microbiology Team Leader |
| Salome Bwayo | Pharmacy Student |
| Kristen Miller, Pharm.D. | Regulatory Project Manager |

**Vicuron Pharmaceuticals, Inc:**

| | |
|---|---|
| Eve Damiano | Vice President, Regulatory Affairs |
| Beth Goldstein (by telephone) | Director, Clinical Microbiology |
| Lisa Goldberg (by telephone) | Senior Clinical Scientist |
| George Horner III | President and Chief Executive Officer |
| Mark Klinger | Senior Management, Regulatory Affairs |
| David Krause, M.D. | Clinical Research/ Medical Affairs |

| | |
|---|---|
| Drew Sansone | Director, Regulatory Affairs & Compliance |
| Jennifer Schranz, M.D. | Director, Clinical Research and Medical Affairs |
| [ ]M.D. | Clinical Consultant [ ] |
| Martin Stogniew, Ph.D. | Executive Vice President, Scientific Affairs |
| [ ] | Hepatic Consultant: [ ] |
| Michele Wible (by telephone) | Director, Biostatistics and Data Management |

**BACKGROUND:**

Vicuron submitted NDA 21-632 for anidulafungin injection for the indication of treatment of esophageal candidiasis on April 25, 2003. On May 21, 2004, the Division issued an approvable letter to Vicuron for NDA 21-632. On December 22, 2004, Vicuron requested a face to face meeting to discuss the future submission plans for anidulafungin for the indications of esophageal candidiasis (EC) and invasive candidiasis (IC). On February 16, 2005, a briefing package was submitted to the Division in preparation for this meeting. On March 17, 2005, the Division responded by fax to the questions in Vicuron's background package.

**DISCUSSION POINTS:**

After introductions, Vicuron and their consultant presented the design and results of studies VER002-9, entitled "Phase 3, Double-Blind, Randomized, Non-inferiority Study of Anidulafungin (100 mg) vs. fluconazole as a Treatment for Patients with Candidemia and/or other forms of Invasive Candidiasis" and VER002-11, entitled "Phase 2 open label study of the Safety and Efficacy of intravenous anidulafungin (50mg) as a Treatment for Azole-refractory mucosal candidiasis" to demonstrate the safety and efficacy of anidulafungin and information on the hepatic safety of anidulafungin [please see attached slides]. The Division asked Vicuron to please provide plot graphs of liver function laboratory data, similar to that presented for patients on anidulafungin, for all patients on fluconazole in studies VER002-4 and VER002-9. Vicuron agreed to submit this information.

Vicuron then acknowledged receipt of the March 17, 2005 fax that contained responses to the questions from the background package. Vicuron accepted the responses for the majority of questions, but requested to further discuss the following questions:

**Question:** Does the Agency concur with the expected role of anidulafungin in the treatment of esophageal candidiasis as described in Section 7.6 and can this expected role form the basis for an indication statement?

> Vicuron proposed the indication "[ ] treatment of [ ] esophageal candidiasis". The Review Team agreed that this was a reasonable start, but that specific wording of the indication will be based upon the review. The Review Team emphasized that Vicuron should clearly address in the clinical studies or the precautions section the hepatic signal and increased relapse rate in the proposed labeling. Vicuron agreed.

**Question:** Does the Agency concur with Vicuron's proposal to submit case report forms for patients who died, patients who had SAEs, and patients who discontinued due to AEs for both the resubmission of the NDA for esophageal candidiasis and the new NDA for invasive candidiasis?

In the March 17, 2005 fax, the Review Team asked Vicuron to please provide CRFs for all patients that experienced serious clinical hepatic events or significantly elevated liver function tests. Vicuron proposed two options regarding the definition of significantly elevated liver function tests. The Review Team stated that further discussion would be needed and that a decision would be made within one week.

**Addendum: On March 28, 2005, the Review Team provided the following response: "Please provide case report forms for all patients with significantly elevated liver function tests defined as two times the upper limit of normal."**

**Question:** Does the Agency concur with Vicuron's proposal (Section 7.7) for submitting a Request for Pediatric Deferral 60 days in advance of the NDA for invasive candidiasis and that the Pediatric Waiver which Vicuron submitted for the original NDA is still in effect for the resubmitted NDA for esophageal candidiasis?

The Review Team stated that consistency should be maintained across the drug class and that after verification, a decision would be sent to Vicuron within one week.

**Addendum: On March 28, 2005, the Review Team provided the following response: The Division acknowledges the pediatric waiver granted for anidulafungin for the indication of esophageal candidiasis. Following resubmission, this waiver will remain in effect for the indication of esophageal candidiasis. The Division agrees with Vicuron's plan to submit a deferral for the pediatric requirement for the invasive candidiasis indication.**

**Question:** Does the Agency concur that, if confirmed upon review, the superiority of anidulafungin vs. fluconazole for the treatment of invasive candidiasis (Study VER002-9 data) represents a significant improvement in medical care compared to a marketed product and may form the basis of granting a priority review for the invasive candidiasis NDA targeted for submission 3Q05?

The Review Team stated that a one to two page summary outlining the support for this request should be included in the cover letter of the NDA submission. The Review Team will review this information in the context of the overall application, and the final decision would be made at filing.

The Review Team asked Vicuron to please provide a timeline for submission. Vicuron stated that the resubmission of NDA 21-632 (EC) is scheduled for mid-May, and that the new NDA for IC is scheduled to be submitted early in the third quarter of 2005. Invasive candidiasis data will be contained in the NDA 21-632 resubmission to support the EC indication; this data will also be incorporated by reference to the IC NDA submission. An additional 33 patients from study VER002-9b will be available to support the IC indication. These patients will be included in the 120-day safety update for the NDA 21-632 resubmission or in the new NDA for IC, depending on the timing of the new NDA submission.

Referring to page 9 of the background package (submitted on February 16, 2005), the Review Team asked Vicuron if there were any plans regarding a refractory indication. Vicuron responded that they are not pursuing a refractory indication, but that study VER002-11 (for treatment of azole-refractory mucosal candidiasis) will be submitted as support in the clinical study section of labeling. The Review Team asked Vicuron to describe the types of patients enrolled in the IC study. Vicuron noted that the patients were very sick with many in medical intensive care units. The Review Team was then asked to comment on the availability of catheter management. Vicuron indicated that information on catheters would be provided, including insertion and removal dates for all catheters, and the investigator's assessment as to whether the infection was regarded as line-associated.

The Review Team asked Vicuron how far out patients were followed for survival. Vicuron responded that patients were followed for 6 weeks, and referenced the Kaplan-Meier plot on page 26 of the February 16, 2005 background package that demonstrates a trend toward increased survival in anidulafungin patients.

Finally, Vicuron noted that real electronic datasets will be submitted approximately one month prior to submission for review by the reviewers. The Review Team agreed to this. Vicuron was thanked for a very effective and productive presentation and meeting.

**ACTION ITEMS**

1. Vicuron will provide plot graphs of liver function laboratory data, similar to that presented for patients on anidulafungin, for all patients on fluconazole in studies VER002-4 and VER002-9.
2. The Review Team will further discuss what should be submitted regarding significantly elevated liver function tests and will respond to Vicuron within one week.
3. The Review Team will verify consistency across the drug class regarding pediatric requirements and respond to Vicuron within one week.
4. Vicuron will submit real electronic datasets approximately one month prior to submission of the NDA.

**Minutes Preparer: Kristen Miller, PharmD, Project Manager**

**Chair Concurrence: Mark Goldberger, M.D., M.P.H, Director ODE IV**

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(4) Draft Labeling

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/s/

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Mark Goldberger
4/20/05 02:49:51 PM

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation IV**

# FACSIMILE TRANSMITTAL SHEET

**DATE:** March 28, 2005

| | |
|---|---|
| **To:** Drew Sansone | **From:** Kristen Miller, Pharm.D. |
| **Company:** Vicuron | Division of Special Pathogen and Immunologic Drug Products |
| **Fax Number:** 610-490-2298 | **Fax Number:** 301-827-2475 |
| **Phone Number**: 610-490-2218 | **Phone Number:** 301-827-2127 |

**Subject:** Response from March 21, 2005 meeting

**Total no. of pages including cover:**

**Comments:**

**Document to be mailed:** ☐ YES ☑ NO

Please refer to our March 21, 2005 meeting where the Division agreed to provide additional information to Vicuron regarding anidulafungin (NDA 21-632) for the indication of treatment of esophageal candidiasis on April 25, 2003. We are provided the following responses and requests for information:

1. The Division acknowledges the pediatric waiver granted for anidulafungin for the indication of esophageal candidiasis. Following resubmission, this waiver will remain in effect for the indication of esophageal candidiasis. The Division agrees with Vicuron's plan to submit a deferral for the pediatric requirement for the invasive candidiasis indication.

2. Please provide plot graphs of liver function laboratory data, similar to that presented for patients on anidulafungin, for all patients on fluconazole in studies VER002-4, entitled "A Phase III, Randomized, Double-Blind, Double-Dummy, Non-Inferiority Study of the Safety and Efficacy of Intravenous Anidulafungin (50mg) Vs. Fluconazole in the Treatment of Patients with Esophageal Candidiasis" and VER002-9, entitled "A Phase III, Double-Blind, Randomized, Multi-center, Study of the Safety and Efficacy of Anidulafungin Vs. Fluconazole in the Treatment of Patients with Candidemia and Other Forms of Invasive Candidiasis and Prevention of Complications."

3. Please provide case report forms for all patients with significantly elevated liver function tests defined as two times the upper limit of normal

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-827-2127 if you have any questions regarding the contents of this transmission.

Kristen Miller, Pharm.D.
Regulatory Project Manager

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/s/

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Kristen Miller
3/28/05 09:43:59 AM
CSO

**Division Director and Deputy Office Director Review**

| | |
|---|---|
| **APPLICANT:** | **Vicuron Pharmaceuticals, Inc.** |
| **DRUG:** | **anidulafungin** |
| **TRADE NAME:** | **[ ] for Injection** |
| **NDA:** | **21-632** |
| **DATE OF SUBMISSION:** | **April 25, 2003** |
| **Major Amendment:** | **January 6, 2004** |
| **PDUFA GOAL DATE:** | **May 25, 2004** |
| **FORMULATION:** | **Intravenous injection (10 mg, 50 mg)** |
| **INDICATION:** | **Treatment of esophageal candidiasis** |

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## A. Recommended Regulatory Action - Approvable

Vicuron submitted NDA 21-632 for [ ] (anidulafungin) for injection and is requesting the indication of esophageal candidiasis. Based on the review of this application, for the reasons summarized below, the applicant should be issued an **approvable** letter.

## B. Summary of Key Findings and Deficiencies

1. Key Findings

   a. The pivotal Phase 3 study VER002-4 comparing anidulafungin to fluconazole shows evidence of a clinical response in the treatment of patients with esophageal candidiasis based upon the response rates that show non-inferiority to comparator at the end of therapy visit (EOT). However, the phase 3 study also shows that the observed response to anidulafungin therapy is not durable; at the follow-up visit (two-weeks after completion of therapy), anidulafungin patients had a higher rate of relapse than comparator treated patients. [For more information, see CLINICAL EFFICACY and REGULATORY BRIEFING overview below.]
   b. The evaluation of the data from the single relatively large (for esophageal candidiasis) adequate-and-well-controlled study in patients with esophageal candidiasis was complicated by the mislabeling of the drug product in 70% of the drug samples. This issue was extensively investigated by the company, the review division and the Division of Scientific Investigation. After a thorough review and reanalysis of the data in the NDA, including an analysis of efficacy in patients who had serum samples assayed for

both anidulafungin and fluconazole and who were found to have only the assigned study drug in serum samples, the division concluded that despite the mislabeling of study drug, the results of the study were not invalidated. The multiple additional analyses that included analyses on the subset of patients whose serum samples were assayed and showed the correct study drug, were consistent with the observed non-inferior response at the end of treatment and the higher rate of relapse at the two-week post treatment visit. In the Agency's analyses of data from the pivotal EC study, the exclusions also included study center 19 because of the relatively frequent detection of both study drugs in serum samples from patients from site 19. [For more information, see DATA INTEGRITY below.]

c. The clinical studies show an apparent dose and duration dependent relationship with IV anidulafungin and elevations in ALT and AST from studies that included higher doses of anidulafungin. Acute and repeat-dose animal studies identified the liver as a target organ of toxicity as shown by slight to moderate hepatic injury with related elevations in ALT and AST levels. In the single pivotal adequate-and-well-controlled trial in patients with esophageal candidiasis, one patient who died had evidence of hepatotoxicity. The assessment of causality in this case was complicated by the patient's underlying medical conditions and concomitant medications, but the contribution of anidulafungin to the observed event could not be excluded. [For more information, see CLINICAL SAFETY summary below, including ODS consult recommendations, PHARMACOLOGY/TOXICOLOGY below.]
d. Given there is evidence of a clinical response to treatment at the end of therapy (EOT) but lack of a durable response at the two-week follow up visit, findings of potential hepatotoxicity, including one patient with other confounding medical conditions and concomitant medications with marked abnormalities of liver function tests who died, the size of the available safety database, the mislabeling of study drugs and subsequent investigations and analyses, the risk-benefit of anidulafungin for esophageal candidiasis does not support approval of this product based upon the currently available data.

2. Deficiencies

The application provides evidence of a clinical response in patients treated with anidulafungin for esophageal candidiasis based upon demonstrating non-inferiority to comparator at the end of therapy visit (EOT) in one relatively large (for esophageal candidiasis) study. However, the relapse rate for anidulafungin treated patients at the two-week post therapy visit was considerably higher than what was observed with comparator therapy. Given the observed benefit of therapy, including the high relapse rate at two-weeks post therapy, the mislabeling of study drug and subsequent investigations, the safety profile from the clinical studies, including the potential for hepatic toxicity, and the relatively limited size of the available safety database at the proposed dose and duration, a satisfactory risk-benefit ratio has not been demonstrated. In order to support the safety and efficacy of the product, additional data should be provided to further characterize the safety profile, including the potential for hepatic toxicity and to support the efficacy of anidulafungin in esophageal candidiasis. In addition, data that would provide stronger evidence of the benefits of anidulafungin in the treatment of esophageal candidiasis could help to offset the risks of therapy including the limited safety experience and attendant uncertainty with regards to the product's safety profile, specifically with regards to hepatic

toxicity. Given the findings with regards to the potential for hepatic toxicity, additional clinical data to characterize the safety and/or additional data that would demonstrate greater benefit in the treatment of esophageal candidiasis are needed in order to achieve a satisfactory risk/benefit profile. In order to address these deficiencies the following types of information will need to be provided in order to further characterize the safety profile and support the efficacy of anidulafungin for esophageal candidiasis.

a. Submit results from one or more additional clinical studies evaluating the safety of intravenous anidulafungin at doses and durations of therapy that are at or above the dose and duration proposed for the treatment of esophageal candidiasis in order to further evaluate the safety profile of anidulafungin, particularly the risk of hepatotoxicity. The additional clinical safety data do not need to be derived from only clinical studies of patients with esophageal candidiasis (e.g., data from patients in a study of invasive candidiasis/candidemia at a dose and duration at or above the proposed dose and duration for esophageal candidiasis would also be acceptable).

b. Submit results from one or more adequate and well-controlled studies to support the efficacy of anidulafungin in the treatment of patients with esophageal candidiasis. This additional supportive data can be derived from the following types of studies:
   - An additional adequate and well-controlled study of esophageal candidiasis to evaluate anidulafungin treatment regimens to improve the durability of response and support the efficacy of anidulafungin in the treatment of patients with esophageal candidiasis. Such a study would need to demonstrate both efficacy at the end of therapy and durability of response at the two-week follow-up to support an unqualified indication of esophageal candidiasis.

   AND/OR
   - An adequate and well-controlled study that supports the efficacy of intravenous anidulafungin in a serious infection due to *Candida* spp. This can be provided by demonstrating efficacy in an adequate and well-controlled study of anidulafungin compared to an approved control drug in systemic Candida infections, such as invasive candidiasis and candidemia. Vicuron's ongoing study VER002-9 comparing anidulafungin to fluconazole in the treatment of patients with candidemia and invasive candidiasis may represent such a study. Because of the higher relapse rate observed at the two-week follow-up visit in study VER002-04, efficacy data from an indication other than esophageal candidiasis may not support an unqualified indication of esophageal candidiasis.

In addition, the Applicant is also encouraged to provide any available data from clinical studies that investigate the role of anidulafungin in the treatment of patients with refractory esophageal candidiasis and/or patients with esophageal candidiasis intolerant of other approved therapies for the treatment of esophageal candidiasis. Such data can help support the risk benefit ratio for anidulafungin. This could include patients that have been enrolled in ongoing studies to date as well as patients who would be enrolled in either of the above named studies.

3. Additional Points for Consideration

a. One possible course of action raised at the Regulatory Briefing is that the application could be presented to the FDA Antiviral Drugs Advisory Committee for discussion. The application could be presented in its current form or alternatively, for a more informed discussion, the application could be presented at the time when the data from the currently ongoing studies in invasive candidiasis / candidemia and fluconazole-refractory mucosal candida infections are available in order to be able to consider additional data to more fully characterize the safety and efficacy of anidulafungin for esophageal candidiasis.
b. To further evaluate the safety, particularly to determine whether a signal of liver injury may be seen in other indications and other dosage regimens, additional data from the studies described in items 2a,b above would be useful in further characterizing the safety and efficacy of anidulafungin for the treatment of esophageal candidiasis. If there are no additional hepatotoxic events, and/or further evidence is presented that demonstrates the efficacy of anidulafungin including improved durability of response, it may be reasonable to consider approval for esophageal candidiasis. Of note is that the drugs currently approved for treatment of esophageal candidiasis and candidemia are associated with hepatotoxicity and carry labeling to that effect. It may be possible to provide information on adverse events associated with anidulafungin in labeling to guide appropriate prescribing. Alternatively, if evidence of significant new hepatotoxicity is identified in these additional trials, the risk/benefit evaluation may not support a decision for approval for esophageal candidiasis.

## C. Summary Review

1. CLINICAL EFFICACY

In NDA 21-632, the applicant (Vicuron) seeks approval for anidulafungin injection in the treatment of esophageal candidiasis. Anidulafungin is a new molecular entity in the echinocandin class of antifungal agents. In support of the proposed indication, the applicant presents data from one relatively large (for esophageal candidiasis), adequate and well-controlled study in patients with esophageal candidiasis with underlying HIV/AIDS in the majority of the patients. The proposed dose and duration is 100 mg of anidulafungin intravenously on the first day of therapy followed by 50 mg intravenously daily for 14 to 21 days (this dosage regimen is abbreviated as "100/50").

In addition to the single large adequate and well-controlled study in patients with esophageal candidiasis, the applicant presents supportive data from three smaller phase 2 studies as follows:

- A dose–ranging study of 36 patients with esophageal candidiasis randomized to receive one of two doses of anidulafungin, either a dose of 50/25 mg or a dose of 70/35 mg IV for a duration of 14 to 21 days. Both doses in this phase 2 study were smaller than the 100/50 mg dose used in the pivotal esophageal candidiasis study (the dose for which the applicant is seeking approval).
- An on-going, open-label, non-randomized study of anidulafungin 100/50 mg IV daily for 14 to 21 days for the treatment of fluconazole-refractory mucosal candidiasis. Data from

5 patients are included in the NDA (2 of these 5 patients had esophageal candidiasis) of a planned total enrollment of 20 patients.

- An open-label, randomized, dose-ranging study that enrolled 120 patients (40 on each of the three arms) with invasive candidiasis (nearly 90% with candidemia alone) treated with anidulafungin doses of 100/50 mg, 150/75 mg, or 200/100 mg intravenously daily for a minimum duration of 14 days and up to 42 days. (The median duration of therapy was 14 days.) Most of these patients were immunocompromised.

Findings from the single large adequate and well-controlled study of esophageal candidiasis shows that anidulafungin met the protocol-specified primary endpoint with 97.4% (225/231) endoscopic success in anidulafungin treated evaluable patients at end of therapy compared to 98.7 % (233/236) for fluconazole (Table 1).

**Table 1: Endoscopic Response at EOT in Clinically Evaluable Population**

| Response | | Anidulafungin IV 100/50 mg QD N= 231 | Fluconazole PO 100 mg QD N= 236 | Treatment difference | 95% CI |
|---|---|---|---|---|---|
| Success n, (%) | | 225 (97.4) | 233 (98.7) | -1.3% | -4.2%, 1.6% |
| | Cure | 204 (88.3) | 221 (93.4) | -5.3% | -10.9%, 0.3% |
| | Improvement | 21 (9.1) | 12 (5.1) | | |
| Failure n, (%) | | 6 (2.6) | 3 (1.3) | | |

Data are from FDA Statistical Reviewer's Analysis. Site 19 excluded.

Based upon available information in the published literature, the success rate in the anidulafungin arm is considerably higher than would be expected for placebo at the end of therapy timepoint.[1,2,3,4]

At the two week post-therapy follow-up visit the endoscopic success rate for anidulafungin was found to be statistically significantly inferior to fluconazole -- 39.0% (90/231) for anidulafungin vs. 69.1% (163/236) for fluconazole. [For more information, see OVERVIEW OF THE CLINICAL PROGRAM below.]

The results of the adequate and well controlled phase 3 EC study show that anidulafungin is effective at the end of treatment (EOT) but this response is not durable. Although a cross study comparison between anidulafungin and caspofungin (the only currently approved echinocandin) is not possible, it can be stated that anidulafungin relapse rate was 30% greater than the fluconazole relapse rate in the Phase 3 trial at 2 weeks. In the caspofungin application and approved product labeling, the relapse rate was 2.7% greater than the comparator (fluconazole

[1] Barbaro G, Barbarini G, Di Lorenzo G. Fluconazole vs. flucytosine in the treatment of esophageal candidiasis in AIDS patients: a double-blind, placebo-controlled study. Endoscopy. 1995 Jun;27(5):377-83.
[2] Barbaro G, Barbarini G, Di Lorenzo G. Fluconazole vs. itraconazole-flucytosine association in the treatment of esophageal candidiasis in AIDS patients. A double-blind, multicenter placebo-controlled study. The Candida Esophagitis Multicenter Italian Study (CEMIS) Group. Chest. 1996 Dec;110(6):1507-14.
[3] Nyst MJ, Perriens JH, Kimputu L, Lumbila M, Nelson AM, Piot P. Gentian violet, ketoconazole and nystatin in oropharyngeal and esophageal candidiasis in Zairian AIDS patients. Ann Soc Belg Med Trop. 1992 Mar;72(1):45-52.
[4] Ravera M, Reggiori A, Agliata AM, Rocco RP. Evaluating diagnosis and treatment of oral and esophageal candidiasis in Ugandan AIDS patients. Emerg Infect Dis. 1999 Mar-Apr;5(2):274-7.

200 mg QD) at 2 weeks after treatment and 11.5% greater than comparator at 4 weeks. (See Table 2 and Table 3 below.) There were differences in the design and conduct of these studies which preclude cross-study comparisons. In the caspofungin study, all caspofungin patients could receive prophylaxis with 100 mg fluconazole and the contribution of prophylaxis on the outcome cannot be excluded. Also noted in the MO review is that after completing treatment, 40/81 (49.4%) caspofungin-treated patients compared to 26/94 (27.7%) of fluconazole-treated patients received antifungal therapy in the follow-up period. In addition, while the difference in relapse rate was considered statistically significant in the anidulafungin trial, the difference in relapse rates in the caspofungin trial was not considered statistically significant.)

**Table 2: Endoscopic Response at Follow-up** in Clinically Evaluable Population**

| | Anidulafungin IV 100/50 mg QD | Fluconazole PO 100 mg QD | Difference (95% CI) | p-value* |
|---|---|---|---|---|
| Sustained Success at follow-up, n/N (%) | 90/231 (39.0) | 163/236 (69.1) | -30.1 (-39.1, -21.1) | <0.0001 |
| Relapse, n/N (%) | 120/225 (53.3) | 45/233 (19.3) | 34.0 (25.3, 42.7) | <0.0001 |
| Relapse or Indeterminate, n/N (%) | 135/225 (60.0) | 70/233 (30.0) | 30.0 (20.9, 39.1) | <0.0001 |

*Fisher's Exact Test
Relapse indicates success at EOT and failure at Follow-up visit
Data are from FDA Statistical Reviewer's Analysis. Site 19 excluded.
** The Follow-Up assessment occurs 2 weeks after the completion of therapy.

**Table 3: Relapse Rates at 14 and 28 Days Post-Therapy in Patients with Esophageal Candidiasis at Baseline**

| | CANCIDAS | Fluconazole | % Difference *(95% CI) |
|---|---|---|---|
| Day 14 post-treatment | 7/66 (10.6%) | 6/76 (7.9%) | 2.7 (-6.9, 12.3) |
| Day 28 post-treatment | 18/64 (28.1%) | 12/72 (16.7%) | 11.5 (-2.5, 25.4) |
| *calculated as CANCIDAS – fluconazole | | | |

One hypothesis that has been brought up is that echinocandins administered intravenously may not be as active against mucosal infections such as oropharyngeal candidiasis and esophageal candidiasis. For example, caspofungin in the treatment of oropharyngeal candidiasis (OPC) was approximately 10% less effective at the completion of therapy and significantly inferior with regards to relapse rates compared to fluconazole. The question of whether either higher doses and/or longer duration of anidulafungin treatment would result in more durable response is worthy of consideration. However, the question of whether increased or longer durations of treatment may also lead to increase in toxicity also needs to be considered, given that results from the pharmacokinetic trial evaluating 260mg followed by 130mg dosing for 10 days showed elevations in liver function tests.

The timing of the test-of-cure assessment is an important point relative to the observed results in the single large pivotal study of esophageal candidiasis. Typically, the test of cure is assessed at a point in time that is the equivalent of several drug half-lives after study drug therapy has been completed. In the current trial, the primary efficacy analysis of Endoscopic Response at the End of Therapy demonstrates non-inferiority of anidulafungin to fluconazole. However, the assessment of the secondary endpoint of Endoscopic Response at Follow-Up demonstrates inferiority of anidulafungin to fluconazole in the single large pivotal study of patients with EC. While the course of esophageal candidiasis in patients with severe and persistent underlying

immune compromise may be one of recurrence, the study demonstrates a differential effect of relapse at the follow-up visit.

Finally, although most of the microbiology information in the application is on fluconazole-susceptible Candida isolates; there was data from 2 patients with esophageal candidiasis due to resistant/refractory Candida species and some data from an animal model. This information is inadequate to conclude that anidulafungin is effective in fluconazole-refractory candida infections. The activity of anidulafungin in fluconazole-refractory candida should be further evaluated.

## 2. CLINICAL SAFETY

The human safety database for anidulafungin comprises data from 461 anidulafungin treated subjects from the Phase 2 and 3 studies in the clinical development program, including 300 patients from the pivotal Phase 3 study. In general, the adverse event rates for anidulafungin in the pivotal Phase 3 study were similar to the control drug, fluconazole, in terms of overall adverse events, drug related adverse events, and discontinuations. [See OVERVIEW OF CLINICAL PROGRAM below.] Preclinical and clinical data did not reveal a signal or evidence of QT prolongation. However, the hepatic findings in preclinical and clinical studies, anidulafungin show findings of potential hepatic toxicity. These findings from review of the hepatic safety data are further discussed below.

Acute and repeat-dose animal studies identified the liver as a target organ of toxicity as shown by slight to moderate hepatic injury with related elevations in ALT and AST levels. [See PHARMACOLOGY/ TOXICOLOGY summary below.] In Phase 1 studies dose-dependent elevations in AST, ALT (levels of AST and ALT elevation were < 3 x ULN) and a dose-dependent elevation of alkaline phosphatase were observed. In study VER 002-5, a phase 1 dose ranging study in healthy subjects, the number of liver-related adverse events reported appeared to be related to the dose received (Table 4).

**Table 4. Most Frequently Reported Adverse Events Presented by Dose Group for Liver-Related Adverse Events**

| **MedDRA Higher Level Term[a]** *Preferred Term* | **Dose Group** | | |
|---|---|---|---|
| | **150 mg/75 mg (Group A)** (n = 10) (n, %) | **200 mg/100 mg (Group B)** (n = 10) (n, %) | **260 mg/130 mg (Group C)** (n = 10) (n, %) |
| Liver Function Analyses | 0 | 3 (30.0) | 5 (50.0) |
| *Alanine Aminotransferase Increased* | 0 | 3 (30.0) | 5 (50.0) |
| *Aspartate Aminotransferase Increased* | 0 | 0 | 3 (30.0) |

Note: A subject who reported the same Preferred Term more than once was counted only once for that Preferred Term. In addition, a subject who reported more than one AE within a specific Higher Level Term was counted only once for that Higher Level Term
Adapted from VER 002-5 Study Report, Table 6.2, p. 61.

Also noted in Study VER002-5 is an apparent temporal association with changes in median values for ALT, AST, and alkaline phosphatase in the group of ten subjects that received a

loading dose of 260 mg followed by 130 mg of anidulafungin IV for 14 days as shown in Table 5 below:

**Table 5. Median changes in ALT, AST and Alkaline phosphatase following anidulafungin 260 mg loading dose and 130 mg daily dose for 14 days**

| Timing of Assessment | Laboratory Analyte | | |
|---|---|---|---|
| | ALT (U/L) | AST (U/L) | Alk Phos (U/L) |
| Baseline | 18.5 | 21.5 | 81.5 |
| Day 3 | 20.5 | 19.5 | 79.0 |
| Day 5 | 24.5 | 22.5 | 76.0 |
| Day 10 | 38.0 | 33.5 | 93.0 |
| Day 14 | 57.0 | 39.0 | 111.0 |

Adapted from VER002-5

Analyses of liver function tests from the pivotal phase 3 esophageal candidiasis study evaluating degrees of elevation of ALT and AST shows a slightly greater proportion of patients with elevated ALT on fluconazole and a slightly greater proportion of patients with elevated AST on anidulafungin. When patients with elevated AST >3 times normal plus bilirubin >1.5, or >2.0 times normal are assessed, the rates are comparable in both arms (Table 6).

**Table 6. Number of Patients with Abnormalities in Pre-Specified Hepatobiliary Parameters at any Time on Therapy**

| Parameter and Limit | Treatment Arm | | | |
|---|---|---|---|---|
| | Anidulafungin N= 300 | | Fluconazole N= 301 | |
| | # Patients | % Patients | # Patients | % Patients |
| ALT > 3 x ULN | 16/283 | 5.6 | 24/282 | 8.5 |
| ALT > 5 x ULN | 5/283 | 1.7 | 7/282 | 2.4 |
| ALT > 10 x ULN | 1/283 | 0.3 | 1/282 | 0.3 |
| ALT > 3 x ULN + bilirubin > 1.5 x ULN | 2/193 | 1.0 | 2/195 | 1.0 |
| ALT > 3 x ULN + bilirubin > 2.0 x ULN | 1/193 | 0.5 | 1/195 | 0.5 |
| AST > 3x ULN | 41/283 | 14.4 | 35/281 | 12.4 |
| AST > 5x ULN | 17/283 | 6.0 | 14/281 | 4.9 |
| AST > 10x ULN | 4/283 | 1.4 | 2/281 | 0.7 |
| AST > 3 x ULN + bilirubin > 1.5 x ULN | 4/193 | 2.0 | 4/195 | 2.0 |
| AST > 3 x ULN + bilirubin > 2.0 x ULN | 2/193 | 1.0 | 3/195 | 1.5 |
| Alkaline phosphatase > 1.5 x ULN | 46/283 | 16.2 | 58/282 | 20.5 |

The adverse event of "liver function tests abnormal" was reported in 10 (3.3%) anidulafungin vs. 4 (1.3%) fluconazole patients, and the adverse event "aspartate aminotransferase increased" was reported in 4 (1.3%) anidulafungin vs. 10 (3.3%) fluconazole patients (see Table 20). The adverse event "aspartate aminotransferase increased" was reported in 4 (1.3%) anidulafungin vs. 10 (3.3%) fluconazole patients (see Table 20). For the patients with the adverse event of "aspartate aminotransferase increased," one of the anidulafungin and 3 of the comparator-treated patients' adverse events were judged to be severe.

In the Phase 2 study of invasive candidiasis where three doses were tested, no dose effect in ALT elevation was seen, although 2/40 (5%) patients in each of the three arms had ALT >3 x ULN and bili >1.5 x ULN. Elevated ALT > 3 x ULN and bilirubin >2.0 x ULN was seen in 1/40, 1/40 and 2/40 patients in the low, mid and high dose, respectively.

In the Phase 3 trial there were 23 deaths (7.7%) on anidulafungin and 20 deaths (6.6%) on fluconazole. One patient death (Patient 13-008, anidulafungin arm) was considered by the investigator to be possibly drug-related. This patient had a history of alcohol abuse, pulmonary tuberculosis, bronchiectasis, and right-sided heart failure and received multiple concomitant medications. He died on the — day of anidulafungin therapy. [See Office of Drug Safety consult March 25, 2004]. In addition, the MO review observes that among the patients who died, 7/23 (30%) anidulafungin and 3/22 (14%) of fluconazole patients had at least one clinically significant liver function test abnormality; all of these, with the possible exception of the patient mentioned above, were considered unrelated to study drug.

The death of patient 13-008 was investigated by the applicant and was also reviewed by an expert hepatologist, Dr. [ ] The assessment of the sponsor and Dr. [ ] notes the risk for ischemic "shock" liver due right heart failure and that the pattern of transaminase elevations is consistent with shock liver. The applicant and Dr. [ ] also note that the pattern does not support an acute drug-induced hypersensitivity reaction given the lack of rash, fever or eosinophilia and that the event was too early for a delayed hepatic idiosyncratic reaction.

A consult was requested from the Office of Drug Safety, on the hepatic safety of anidulafungin and particularly an assessment of the possible association between anidulafungin and patient 13-008 who died, as well as an evaluation of postmarketing safety information on caspofungin and association with acute fulminant hepatic failure. [See ODS consults dated March 18 and March 25, 2004]. None of the medications that patient 13-008 was receiving could easily explain the patient's hepatic event. Patient 13-008 reportedly was chronically ill and had right sided heart failure. The terminal event may have been cardiac in nature, and the case may represent a possible hepatotoxicity due to anidulafungin. The ODS consult also identified 8 cases of hepatotoxicity that were identified in the AERS postmarketing database in patients who had received caspofungin. These cases were complex and challenging to assess with regards to underlying etiology for hepatotoxicity. In four of the caspofungin-associated cases, the onset of LFT abnormalities was within days of starting caspofungin.

3. CHEMISTRY

There are no outstanding CMC issues with this intravenous product

4. MICROBIOLOGY

There are no outstanding issues. The product is active against *Candida albicans* species, the most common cause of esophageal candidiasis. The application contains small numbers of non-albicans species, and 2 patients with fluconazole-refractory candida esophagitis. The data on non-albicans species of *Candida* is not adequate to support any specific labeling statements.

5. CLINICAL PHARMACOLOGY:

There are no outstanding issues and from the standpoint of clinical pharmacology, the application is approvable.

6. PHARMACOLOGY/TOXICOLOGY:

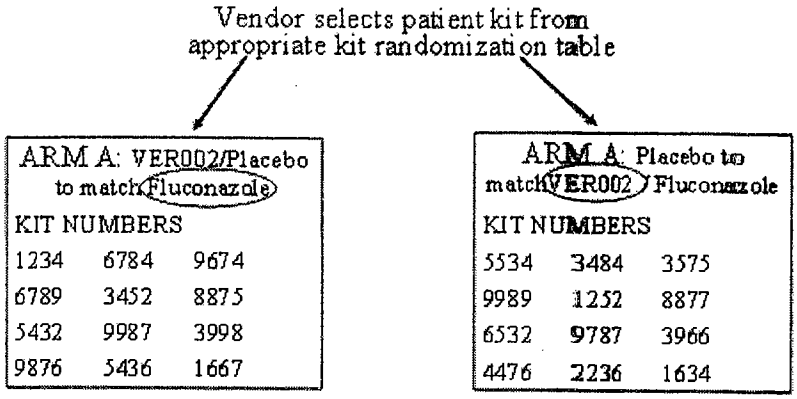
There are no outstanding issues. Animal studies show a signal for hepatotoxicity, including elevations in liver function tests, hepatocellular changes including single cell necrosis, and persistence of hepatic findings after a recovery period. Based on comparison of hepatotoxicity to exposure in animals, anidulafungin does not appear to be more hepatotoxic in preclinical studies than the other two echinocandins tested: caspofungin (approved as Cancidas) and micafungin (currently in development).

In rats ALT and AST elevations up to 5 times normal were seen at doses 1.5 - 10 times human exposure and liver weights were increased. In 13-week rat studies, ALT and AST elevations were seen at end of treatment at levels approximately 10 times human exposure and histologic findings of single cell necrosis accompanied these laboratory findings. One group of rats was followed through a one-month recovery period and noted to have resolution of LFTs and findings of hypertrophy of hepatocytes. An interpretation of this finding is not provided, but one possibility may be a regenerative or reactive process. In a 4-week monkey study at levels 5 times human exposure the animals developed elevations in ALT and AST but no abnormalities on histologic evaluation were noted.

7. DATA INTEGRITY

The applicant identified a problem with mislabeling of the study drugs for the single pivotal esophageal candidiasis study before the study results were unblinded, 5 months before NDA submission, and notified the Division. Therefore, the Division of Scientific Investigations was consulted early in the review on the issue of mislabeling of investigational drugs, and proceeded to investigate and to evaluate their findings. [See Division of Scientific Investigations consult March 24, 2004.]

The issue of mislabeling came to the company's attention in the following way: During the study, patients at selected centers had serum samples obtained for population pharmacokinetic analysis. These serum samples were sent to an independent contract laboratory for analysis and the laboratory – having the randomization schedule – assayed the samples from patients randomized to anidulafungin; these assays showed no detectable anidulafungin, prompting an investigation. The investigation revealed that at the vendor responsible for packaging and distributing products to study sites, a systematic error occurred, that affected 70% of the study patients. Packages containing anidulafungin (VER002) and placebo for fluconazole OR placebo for anidulafungin and active for fluconazole were switched because the wrong "drug" was circled in the header (see diagram below).




**Master Kit Randomization Table**

**Master Kit Randomization Table**

Because the information on the systematic error in randomization was know at the time of the NDA submission, the Division of Scientific Investigations was promptly consulted and undertook inspection of the parties involved in drug distribution and assay of serum samples.

The laboratory analyzed serum samples for 274/601 (46%) of the patients in the study and found agreement with the sponsor's proposed corrected treatment assignment for the subgroup of patients in the sites that received the mislabeled drug. Once all the data were collected, it was observed that there were also 30 patients identified who had drug levels for both anidulafungin and fluconazole present. Fifteen of these patients were in site 19 (total enrolled at site 19 was 47 patients), the other 15 patients were from 7 additional study sites. (Efficacy analyses that excluded data from Center 19 were conducted and the overall results of the analyses were consistent with the analyses that included Center 19.) For these 30 patients, samples were available from days 3, 7 and 14 of study, and the presence of both anidulafungin and fluconazole was generally detected in one of the three samples. Several patients in site 19 had both drugs present on 2 or 3 of the sampled days.

Information about the randomization error and the finding of anidulafungin and fluconazole in patients was presented by DSI at the February 20, 2004 Regulatory Briefing. DSI concluded that the finding of both drugs appeared to be real, suggesting a systematic procedural issue, 11% of patients had both drugs present and this was found in 8 of the 20 study centers in the trial. DSI expressed concern that there is no assurance that 54% of the subject data are free from randomization error and was not confident that the data are reliable. These same concerns were also included in the consult provided by DSI to DSPIDP on March 24, 2004.

Therefore, the Division was asked to address these concerns, including the specific question whether an analysis had been performed that included only the patients that are known (by PK analysis) to have only received the one assigned study drug. Both before and after the

Regulatory Briefing, the clinical pharmacology, statistical and clinical reviewers in the division examined the data in great detail and performed the requested analyses, as well as a range of other analyses (patients from centers with randomization error vs. centers without randomization errors, patients from all centers, patients from site 19 excluded, patients with serum drug levels measured, patients without serum drug levels measured, as well as some elaborate statistical sampling procedures) and all of these analyses evaluating these different subsets yielded results consistent with the overall study analyses. The resulting conclusion by the review staff was the efficacy results were robust, supporting the observed response rates at the end of treatment and confirming a statistically significant difference in relapse rates at two weeks.

8. REGULATORY BRIEFING – February 20, 2004 [See minutes of this meeting.]

Because of the novel challenges encountered during the review of this application, the division presented information on the randomization problem, the efficacy findings and safety at the February 20, 2004 Regulatory Briefing and asked the committee to provide input on the weight of evidence in the application and discuss following questions (see also minutes of Regulatory Briefing):

1. The sponsor has developed a corrected treatment assignment code for patients that the sponsor determined were at risk for systematic misassigment of study drug and has found concordant serum drug levels in the subset of patients for whom testing was available. Do these efforts satisfactorily address the issue of "misassignment" of study drug in the pivotal study? In addition, does the finding of 30 patients with at least one sample containing both drugs (anidulafungin and fluconazole) and the fact that 54% of the patients did not have serum levels measured change this conclusion?

   *The findings by DSI and their recommendations are included in the consult* [See DATA INTEGRITY above.] *and the additional evaluations by the division are summarized in the Statistical Review by Dr. Dixon and the Medical Officer Review by Dr Ibia.*

2. The sponsor provides data from one large (for esophageal candidiasis) adequate and well-controlled study and supportive data from the three described phase 2 studies. The issues of outcome at the end of treatment as well as 2 weeks later, timing of the primary endpoint assessment, safety profile, systematic "misassignment" of study medication resulting in a corrected medication assignment code, and exclusion of Center 19 have been discussed. Are the data in the package sufficiently robust to provide substantial evidence of safety and efficacy anchored in the one large pivotal clinical study?

   *The committee concluded that anidulafungin is clearly more effective than placebo, and that compared to fluconazole, relapse rates were clearly higher, an undesirable outcome that could reflect use of too low a dose. At present it seems hard to argue that anidulafungin is not inferior to the control at the end of therapy visit. The Division needs to decide how important that is. Note was also made that a low dose of the control was used. Conceivably, the drug could be labeled for fluconazole failures. Although there is high relapse, this may be more desirable than more dangerous toxicities, especially if the EC is*

*only mild. When patients relapsed, they relapsed back to baseline or worse, significantly more often than patients on fluconazole. One possible explanation is the presence of oral candidiasis, which was not looked at in a systematic fashion*

*Another factor is the risk of liver toxicity vs. the potential toxicities of other therapies. The one patient who died of hepatotoxicity was discussed and the case was considered confounded because of other components in the patient's medical history including congestive heart failure, prior history of tuberculosis and alcohol, and use of multiple other medications.*

*Based on analysis of the information provided by the sponsor and DSI, and multiple analyses of the study results, the Review Team feels comfortable with the database. Anidulafungin is effective. The Division must determine what the standard for approval in this case should be. The antimicrobial divisions almost always look at drugs compared to an active control, usually insisting that even modest inferiority be ruled out because the consequences of drug failure matter a lot. If the Division felt that it was critical to compare this medication to an active control, it must have felt that the comparative effect mattered. As a general matter, drugs can be approved when they are inferior to other drugs but we would not do this if the lesser effectiveness represented a risk. If the risk were small or non-existent, e.g., delay of improvement of a symptom, approval would be usual, perhaps with labeling pointing out inferiority, if well established. If there were a toxicity concern too, that would argue against approval of a less effective product, unless there were still safety advantages over alternatives. The hepatic toxicity issue must be addressed thoroughly. Every patient's labs should be examined to determine the number of patients that have high bilirubin and transaminases, but have normal alkaline phosphate.*

*One final issue to weigh is the slow down of antibiotic and antifungal development. The FDA must balance between setting standards so high that companies stop development, and becoming so lax as to spark safety concerns.*

*Lastly consideration may be given to issuing a non-approval or approvable, and providing a public hearing to gain community feedback.*

9. RISK BENEFIT

The information on efficacy and safety was reviewed and discussed, and these topics were discussed at the Regulatory Briefing. The efficacy results demonstrated the product was comparable to the control drug at the end of therapy and better than what would be expected with placebo; however, the relapse rate within 2 weeks was 30% greater than for the control. In addition one patient on the anidulafungin arm who died with multiple underlying medical problems had an ALT value of 4168 U/L and AST value of 7058 U/L after three days of anidulafungin therapy following normal baseline values; that this event may possibly represent hepatotoxicity due to anidulafungin cannot be excluded. [See ODS consult March 25, 2004.] In evaluation of the preclinical and clinical data in the NDA, there are laboratory findings that signal the potential for anidulafungin to cause hepatotoxicity. The evaluation of laboratory

changes for AST and ALT in the patients in the single pivotal study finds results that are similar between anidulafungin and comparator. The 2-3 fold apparent dose and duration related increases in ALT and AST seen in patients in study VER002-5 receiving 260/130 anidulafungin cannot be dismissed and further evaluation is necessary. The finding of postmarketing adverse event reports with caspofungin suggests that hepatic toxicity may be associated with echinocandins. However, because of the multiple underlying medical conditions in the patients in whom these events occurred, the role of the echinocandin cannot be precisely assessed. If it is determined that anidulafungin has a higher incidence of serious hepatotoxicity compared to other antifungal products, it would be difficult to recommend approval. At this time, the evaluation of benefit (efficacy at the end of treatment but higher rate of relapse) and the potential signal of hepatotoxicity (an apparent dose and duration related elevation in LFTs in patients in VER002-5 and the possible role of anidulafungin in causing hepatotoxicity in one patient in study VER002-4) precludes recommending approval.

## C. OVERVIEW OF THE CLINICAL PROGRAM ANIDULAFUNGIN FOR THE INDICATION OF ESOPHAGEAL CANDIDIASIS

The NDA database is summarized in Table 7.

**Table 7: Descriptive Summary of Clinical Efficacy Studies**

| Protocol # (Phase) | Objective | Design | Treatment | Primary Endpoint |
|---|---|---|---|---|
| **Pivotal Esophageal Candidiasis Study** | | | | |
| **VER002 -4 (3)** | Safety and efficacy in esophageal candidiasis compared to fluconazole | Randomized, controlled, double-blind, double-dummy, non-inferiority<br><br>N = 601 | IV Anidulafungin 100/50 mg for 14-21 days Vs PO Fluconazole 200/100 mg for 14-21 days<br>Follow-up 14 days post-therapy | Endoscopic response at EOT in clinically evaluable population |
| **Supportive Studies in Esophageal Candidiasis** | | | | |
| **XBAF (2)** | Safety and efficacy in esophageal candidiasis | Open label, randomized dose-ranging<br><br>N = 36 | Anidulafungin 70/35 mg IV or 50/25 mg IV for 14-21 days<br>Follow-up 4 weeks ± 7 days post –therapy | Clinical response at EOT in clinically evaluable population. A post hoc analysis was done using endoscopic response at EOT |
| **VER002 -11 (2/3)** | Safety and efficacy in patients with fluconazole-refractory mucosal candidiasis | On-going open-label, non-randomized study<br>N = 5<br>(of the 5 patients, 2 had esophageal candidiasis) | Anidulafungin 100/50 mg IV for 14-21 days | OPC: Clinical Response at EOT in clinically evaluable population.<br>EC: Endoscopic response at EOT in clinically evaluable population. |
| **Other Supportive Studies** | | | | |
| **VER002 -6 (2)** | Safety and efficacy in patients with invasive candidiasis (this study enrolled primarily patients with candidemia) | Open label, randomized, dose-ranging<br><br>N = 120 | IV Anidulafungin 100/50 mg, 150/75 mg, and 200/100 mg for 14-42 days<br>Follow-up 14 days post-therapy | Global response (clinical and mycologic) 2 weeks post EOT in evaluable at follow-up population |

**1. Pivotal Esophageal Candidiasis Phase 3 Study (VER002-4)**

Study VER002-4 is a phase 3 randomized, double-blind, double-dummy, non-inferiority study of the safety and efficacy of intravenous anidulafungin versus oral fluconazole. The anidulafungin dose was a 100 mg IV loading dose on day one followed by a dose of 50 mg IV daily. Fluconazole was administered at a dose of 100 mg orally daily. This study treated adult patients with esophageal candidiasis for a minimum of 14 days and a maximum of 21 days.[5] Patients underwent endoscopy at baseline and at defined end of therapy (EOT) and follow-up (FU) visits. (Note: follow-up visits occurred two weeks after the completion of therapy.)

A total of 601 patients were enrolled. Of the 47% of patients who agreed to be tested, about 85% tested HIV positive. Tuberculosis was frequent in this population and 27% of patients were on active treatment for tuberculosis. Less than 2% had received prior treatment with fluconazole for esophageal candidiasis. Of the 601 patients enrolled, 488 (81.2%) completed study. The main reason for study discontinuation was adverse events. Of the 601 randomized, 504 (83.4%) were clinically evaluable at the end of therapy. The main reasons for being unevaluable at end of therapy were less than 10 days of therapy and use of systemic antifungal therapy during study period (for reasons other than treatment failure). Rates of premature discontinuation and clinical unevaluability at the end of therapy were balanced between the two groups.

The primary efficacy outcome was defined as endoscopic success at EOT in the clinically evaluable population (Table 8). The proportion of patients achieving success (cure + improvement) at the end of therapy is similar between anidulafungin and comparator. Examination of the proportion of patients that are improvements rather than cures finds that 9.1% of the anidulafungin treated patients were categorized as experiencing improvement, whereas 5.1% of comparator-treated patients were categorized as improvement.

**Table 8: Endoscopic Response at EOT in Clinically Evaluable Population**

| Response | | Anidulafungin IV 100/50 mg QD N= 231 | Fluconazole PO 100 mg QD N= 236 | Treatment difference | 95% CI |
|---|---|---|---|---|---|
| Success n, (%) | | 225 (97.4) | 233 (98.7) | -1.3% | -4.2%, 1.6% |
| | Cure | 204 (88.3) | 221 (93.4) | -5.3% | -10.9%, 0.3% |
| | Improvement | 21 (9.1) | 12 (5.1) | | |
| Failure n, (%) | | 6 (2.6) | 3 (1.3) | | |

Data are from FDA Statistical Reviewer's Analysis. Site 19 excluded..

Endoscopic response at follow-up (2 weeks post therapy) in the clinically evaluable population was one of the secondary endpoints. The results were also calculated for the intent to treat population. Because the results were consistent between these two populations, only the evaluable population results are presented (Table 9). There was a concern with the data from one

[5] Note the DIFLUCAN (fluconazole) product label states the following in the Dosage and Administration section of the label for treatment of esophageal candidiasis: "*Esophageal candidiasis*: The recommended dosage of DIFLUCAN for esophageal candidiasis is 200 mg on the first day, followed by 100 mg once daily. Doses up to 400 mg/day may be used, based on medical judgment of the patient's response to therapy. Patients with esophageal candidiasis should be treated for a minimum of three weeks and for at least two weeks following resolution of symptoms."

site (Site 19) in this study. The results show that anidulafungin is non-inferior to fluconazole at the EOT visit (delta –10%) whether or not site 19 is excluded.

**Table 9: Endoscopic Response at Follow-up** in Clinically Evaluable Population**

| | Anidulafungin IV 100/50 mg QD | Fluconazole PO 100 mg QD | Difference (95% CI) | p-value* |
|---|---|---|---|---|
| Sustained Success at follow-up, n/N (%) | 90/231 (39.0) | 163/236 (69.1) | -30.1 (-39.1, -21.1) | <0.0001 |
| Relapse, n/N (%) | 120/225 (53.3) | 45/233 (19.3) | 34.0 (25.3, 42.7) | <0.0001 |
| Relapse or Indeterminate, n/N (%) | 135/225 (60.0) | 70/233 (30.0) | 30.0 (20.9, 39.1) | <0.0001 |

*Fisher's Exact Test
Relapse indicates success at EOT and failure at Follow-up visit
Data are from FDA Statistical Reviewer's Analysis. Site 19 excluded.
** The Follow-Up assessment occurs 2 weeks after the completion of therapy.

Clinical outcomes and mycologic outcomes closely parallel the above endoscopic outcomes as shown in Table 10, Table 11, Table 12, and Table 13 below. The data in Table 12 shows that the Clinical Response at Follow-up in the Clinically Evaluable at EOT population corroborates the finding of Endoscopic Response at Follow-up in the Clinically Evaluable Population. Similar findings of the lack of a durable response in a considerable proportion of anidulafungin treated patients is also observed in the Per-Patient Mycological Outcomes and Responses in Mycologically Evaluable Populations at Follow-up (Table 13).

**Table 10. Clinical Response at EOT in Clinically Evaluable at EOT Population**

| Response | | Anidulafungin IV 100/50 mg QD N= 231 | Fluconazole PO 100 mg QD N= 236 |
|---|---|---|---|
| Success n, (%) | | 229 (99.1) | 235 (99.6) |
| | Cure | 225 (97.4) | 231 (97.9) |
| | Improvement | 4 (1.7) | 4 (1.7) |
| Failure n, (%) | | 2 (0.4) | 1 (0.1) |

Data are from FDA Statistical Reviewer's Analysis. Site 19 excluded.

**Table 11. Clinical Response at EOT in the All Treated Population**

| Response | | Anidulafungin IV 100/50 mg QD N= 276 | Fluconazole PO 100 mg QD N= 278 |
|---|---|---|---|
| Success n, (%) | | 242 (87.7) | 247 (88.8) |
| | Cure | 237(85.9) | 242 (87.1) |
| | Improvement | 5 (1.8) | 5 (1.8) |
| Failure n, (%) | | 6 (2.2) | 3 (1.1) |
| Indeterminate | | 28 (10.1) | 28 (10.1) |

Data are from FDA Statistical Reviewer's Analysis. Site 19 excluded.

**Table 12. Clinical Response at Follow Up in Clinically Evaluable at EOT Population**

| | **Anidulafungin IV 100/50 mg QD** | **Fluconazole PO 100 mg QD** |
|---|---|---|
| Sustained success | 120/231 (51.9) | 181/236 (76.7) |
| Relapse | 93/229 (40.6) | 30/235 (12.8) |
| Relapse + indeterminate | 109/229 (47.6) | 54/235 (23.0) |

Analysis by FDA Statistical Reviewer. Site 19 excluded.

**Table 13. Per-Patient Mycological Outcomes and Responses in Mycologically Evaluable Populations**

| | | | **Anidulafungin IV 100/50 mg QD** | **Fluconazole PO 100 mg QD** |
|---|---|---|---|---|
| End of Therapy | N | | 180 | 186 |
| | Success | | 156 (86.7) | 169 (90.9) |
| | | Proven eradication | 152 (84.4) | 156 (83.9) |
| | | Presumed eradication | 3 (1.7) | 4 (2.2) |
| | | Colonization | 1 (0.6) | 9 (4.8) |
| | Failure | | 24 (13.3) | 17 (9.1) |
| | | Proven persistence | 23 (12.8) | 12 (6.5) |
| | | Presumed persistence | 0 | 0 |
| | | Superinfection | 1 (0.6) | 5 (2.7) |
| Follow-up | N | | 168 | 167 |
| | Success | | 75 (44.6) | 121 (72.5) |
| | | Proven eradication | 72 (42.9) | 115 (68.9) |
| | | Presumed eradication | 2 (1.2) | 2 (1.2) |
| | | Colonization | 1 (0.6) | 4 (2.4) |
| | Failure | | 93 (55.4) | 46 (27.5) |
| | | Proven persistence | 10 (6.0) | 6 (3.6) |
| | | Presumed persistence | 4 (2.4) | 0 |
| | | Proven recurrence | 66 (39.3) | 34 (20.4) |
| | | Presumed recurrence | 1 (0.6) | 0 |
| | | Superinfection | 12 (7.1) | 6 (3.6) |

Source: Applicant's Submission (NDA 21-632, Study VER002-4 Table 26 of Study Report). Site 19 not excluded.

## 2. Phase 2 Dose Ranging Esophageal Candidiasis Study (H4A-MC-XBAF)

This was a phase 2, randomized, open-label, non-comparative, multicenter study to evaluate the safety and efficacy of two intravenously administered 14- to 21-days dosage regimens of anidulafungin in the treatment of patients (≥ 12 years old) with esophageal candidiasis co-infected with HIV. The two dose regimens studied were: an intravenous loading dose of 50 mg on first day followed by daily intravenous maintenance infusions of 25 mg (50/25 mg dose) and an intravenous loading dose of 70 mg followed by daily intravenous maintenance infusions of 35 mg (70/35 mg dose). Both doses studied in this dose ranging study are lower than the 100 mg/50 mg IV dose studied in the Phase 3 clinical trial and the 100/50 mg IV dose recommended in the company's proposed labeling for this product. The follow-up assessment was done at four weeks (± 7 days) post-therapy or earlier if clinically relapsed. Endoscopy at the follow-up visit was only performed if clinically relapsed. A total of 19 and 17 patients were enrolled in the 50/25 mg and 70/35 mg dose groups, respectively.

The primary objective of the study was to evaluate the safety and efficacy of two intravenous dose regimens of anidulafungin in the treatment of patients with esophageal candidiasis. The

secondary objectives were to evaluate the mycologic response of the two dose regimens, identify potentially efficacious dose regimen for future trials in patients with candidiasis, and to determine PK characteristics of anidulafungin in this patient population and attempt to correlate PK with efficacy and safety outcomes. The primary efficacy outcome in this study was clinical response at EOT in clinically evaluable patients shown in Table 14. Patients with complete resolution of symptoms were considered Cured, those with partial resolution were considered Improved. The clinical success rates at the EOT visit in the 50/25 dose group was 16/16 (100%) compared to the 70/35 dose group (higher dose group) which had a success rate at EOT of 9/11 (81.8%). Clinical Success rates at the follow up visit at 4 weeks (+ 7days) after treatment for the evaluable population are shown in Table 15. Within the limited number of patients in this phase 2 study, the results show a lack of durability of response at the follow-up time point for both dose groups.

**Table 14: Clinical Success at EOT in Evaluable Patients in Study XBAF**

| Anidulafungin IV Dose Group | Clinical Outcome in Evaluable Patients n/N (%) | | |
|---|---|---|---|
| | Cured | Improved | Success |
| 50/25 mg | 11/16 (68.8) | 5/16 (31.3) | 16/16 (100) |
| 70/35 mg | 9/11 (81.1) | 0/11 (0.0) | 9/11 (81.8) |

Success = clinical response of cured (absence of symptoms) or improvement
Source: Adapted from Applicant's submission Tables XBAF 11.11-11.14

**Table 15: Clinical Success at Follow up in Evaluable Patients in Study XBAF**

| Anidulafungin IV Dose Group | Evaluable Patients |
|---|---|
| | Follow-up n/N (%) |
| 50/25 mg QD | 6/16 (37.5) |
| 70/35 mg QD | 6/11 (54.5) |

Success = clinical response of cured (absence of symptoms) or improvement
Source: Adapted from Applicant's submission Tables XBAF 11.11-11.14

In this phase 2 esophageal candidiasis study, endoscopy was required at baseline and at EOT but was repeated at the follow-up visit only in the event of clinical relapse. To reflect the primary endpoint in Study VER002-4, the sponsor performed additional analysis post hoc to assess the proportion of patients with endoscopic cure or improvement in the two dose groups. All treated patients with baseline and EOT endoscopy were included in the analysis. Evaluability criteria were similar to those in the original analysis. In the applicant's analysis success was defined as complete cure and improvement in endoscopic grade. Endoscopic success in the evaluable population is summarized in Table 16. Endoscopic success rates were 11/14 (78.6%) for the 50/25 dose group and 8/9 (88.9%) in the 70/35 (higher dose) group.

**Table 16: Endoscopic Success at EOT in Evaluable Patients**

| Anidulafungin IV Dose Group | Endoscopic Success in Evaluable Patients n/N (%) | | |
|---|---|---|---|
| | Cured | Improved | Success |
| 50/25 mg | 7/14 (50.0) | 4/14 (28.6) | 11/14 (78.6) |
| 70/35 mg | 7/9 (77.8) | 1/9 (11.1) | 8/9 (88.9) |

Source: Adapted from NDA Table XBAF (1a) Page 3 of Study H4A-MC-XBAF

## 3. Phase 2/3 Fluconazole-Refractory Mucosal Candidiasis Study (VER002-11)

This study is ongoing. The objective is to evaluate the safety and efficacy of anidulafungin 100/50 mg IV for 14-21 days in patients with fluconazole-refractory mucosal candidiasis. The sponsor plans to enroll 20 patients. Preliminary results from 5 patients (2 with esophageal candidiasis) were submitted in the NDA. Both esophageal candidiasis patients were endoscopic successes at EOT and clinical cures at follow-up. Nevertheless, the data are limited and do not allow a definitive assessment of anidulafungin in patients with fluconazole-refractory mucosal candidiasis.

**4. Phase 2 Invasive Candidiasis (Primarily Candidemia) Study (VER002-6)**

In study VER002-6, adult patients were randomly assigned to one of the three dose regimens, 100 mg, 150 mg, or 200 mg initial IV loading dose on Day 1 followed respectively by 50 mg, 75 mg, or 100 mg IV daily maintenance dose from Day 2 to a maximum duration of treatment of 42 days, although the average duration of treatment was approximately 14 days. A post-therapy follow-up evaluation was done 2 weeks after end-of-therapy or earlier in the event of failure or use of another systemic antifungal agent.

A total of 123 patients were randomized. A total of 120 patients were treated (40 patients per dose regimen) and 68 (56.7%) of 120 treated patients completed the study. The median age of the 120 patients treated was 54 years and 56.7% were females. Most patients were immunocompromised and relevant baseline medical conditions were similar across the three dose groups. Of the 116 MITT patients, 104 (89.7%) had only candidemia. Twelve patients had invasive candidiasis as documented by tissue samples positive for candidal invasion.

The primary endpoint was the clinical response at follow-up (2 weeks after completing therapy) in the evaluable at follow-up population as summarized in Table 17.

**Table 17: Clinical Response at Follow-Up in Evaluable at FU Population**

| Outcome | Anidulafungin IV Dose | | | Total [N=68] |
|---|---|---|---|---|
| | 100/50 mg QD [N=18] | 150/75 mg QD [N=26] | 200/100 mg QD [N=24] | |
| Success (n, %) | 13( 72.2) | 22( 84.6) | 20( 83.3) | 55( 80.9) |
| Cure (n, %) | 12( 66.7) | 22( 84.6) | 20( 83.3) | 54( 79.4) |
| Improvement (n, %) | 1( 5.6) | 0 | 0 | 1( 1.5) |
| Failure (n, %) | 5( 27.8) | 4( 15.4) | 4( 16.7) | 13( 19.1) |
| Failure (n, %) | 3( 16.7) | 3( 11.5) | 3( 12.5) | 9( 13.2) |
| Worsening of EOT Cure or Improvement | 1( 5.6) | 1( 3.8) | 1( 4.2) | 3( 4.4) |
| Unable to Determine (n, %) | 1( 5.6) | 0 | 0 | 1( 1.5) |

Source: Adapted from Table 5.5 of Study Report for Study VER-002-6 from Applicant's submission

The findings regarding the primary efficacy endpoint including confidence intervals are provided in Table 18. Global Response in the Evaluable Population at Follow-Up, were that the majority of patients in all dose groups had responses of success and that there was a trend for greater efficacy in the two highest dose groups, for which success rates were numerically larger, compared to the 100/50 mg dose group. The confidence intervals for the success rates for each of the three dose groups in this phase 2 study were noted to overlap broadly.

**Table 18. Global Response (Success) at Follow-Up (Evaluable at Follow-up Population)**

| | Dose Group | | |
|---|---|---|---|
| **Statistics** | **100 mg/50 mg** | **150 mg/75 mg** | **200 mg/100 mg** |
| | **(N=18)** | **(N=26)** | **(N=24)** |
| n*/N** (%) | 13/18( 72.2) | 22/26( 84.6) | 20/24( 83.3) |
| 95% CI | 51.5, 92.9 | 70.7, 98.5 | 68.4, 98.2 |

n* =Number of patients with global response of success.
N**=Number of patients in the dose group.
Source: adapted from the Applicant's Table 5.3, p. 72 of the VER002-6 Study Report NDA 21-632

The response rate at EOT a secondary endpoint, for the evaluable population in this phase 2 invasive candidiasis study is shown in Table 19.

**Table 19: Clinical Outcome in Evaluable Patients at EOT in Study VER002-6**

| **Outcome** | **Anidulafungin IV** | | | **Total [N=83]** |
|---|---|---|---|---|
| | **100/50 mg [N=25]** | **150/75 mg [N=30]** | **200/100 mg [N=28]** | |
| Success (n, %) | 22 (88.0) | 27 (90.0) | 25 (89.3) | 74 (89.2) |
| Cure (n,%) | 19 (76.0) | 24 (80.0) | 20 (71.4) | 63 (75.9) |
| Improvement (n, %) | 3 (12.0) | 3 (10.0) | 5 (17.9) | 11 (13.3) |
| Failure (n, %) | 3 (12.0) | 3 (10.0) | 3 (10.7) | 9 (10.8) |
| Failure (n, %) | 3 (12.0) | 3 (10.0) | 3 (10.7) | 9 (10.8) |

Source: Adapted from Table 5.5 of Study Report for Study VER-002-6 from Applicant's submission

## 5. Summary of Efficacy of Anidulafungin in Esophageal Candidiasis

At the end of therapy in the single relatively large (for esophageal candidiasis) pivotal EC study (VER002-4), endoscopic, clinical, and mycologic responses of the patients who received anidulafungin 100/50 mg intravenously daily are comparable to those of patients who received oral fluconazole 100 mg daily for the treatment of esophageal candidiasis at the End of Therapy visit. Given that studies in the medical literature have shown that spontaneous resolution of esophageal candidiasis occurs infrequently in a largely untreated population of patients with AIDS, anidulafungin appears to be better than placebo at the EOT timepoint. However, at the follow-up timepoint 2 weeks post-therapy, a difference was shown between treatment arms with anidulafungin treated patients experiencing a higher relapse rate compared to the fluconazole treated patients in the proportion of patients who were successes at the end of therapy.

Exactly why the efficacy of anidulafungin is not sustained is unclear. Possible explanations include that the molecule is intrinsically less active or that the dose selected may be suboptimal. Examination of the results for endoscopic response at the end of therapy reveals that a slightly higher proportion of patients only achieve improvement rather than cure at the end of therapy visit. The applicant attributes it to a possible class effect of the echinocandins.

## 6. Safety of Anidulafungin

A total of 660 subjects (patients or healthy subjects) received IV anidulafungin within the IV anidulafungin development program. Of these 660 subjects, 412 subjects (62.4%) received a maintenance dose of $\geq$50 mg for at least 10 days and 331 of these subjects (a subset of the 412 subjects) received at least 14 days of IV anidulafungin. Because of differences in study design,

anidulafungin dose, and study population among the four clinical studies, the safety data presented herein focuses on comparison with fluconazole from the pivotal esophageal candidiasis study.

A summary of all treatment-emergent adverse events occurring in at least 10 patients in a treatment group is shown in Table 20 and the overall summary of adverse events is shown on Table 21. The percentage of patients experiencing at least one adverse event is similar for anidulafungin and comparator (fluconazole).

**Table 20: Treatment-Emergent Adverse Events Occurring in ≥ 10 Patients in a Treatment Group in the Pivotal Esophageal Candidiasis Study**

| | Treatment Arm, n (%) | |
|---|---|---|
| | **Anidulafungin IV 100/50 mg QD N= 300** | **Fluconazole PO 100 mg QD N= 301** |
| Number of patients with at least one AE | 237 (79.0) | 226 (75.1) |
| **Preferred Term** | | |
| Pyrexia | 26 (8.7) | 26 (8.6) |
| Headache NOS | 25 (8.3) | 20 (6.6) |
| Diarrhea NOS | 23 (7.7) | 24 (8.0) |
| Vomiting NOS | 20 (6.7) | 28 (9.3) |
| Nausea | 19 (6.3) | 22 (7.3) |
| Dyspepsia | 18 (6.0) | 15 (5.0) |
| Phlebitis NOS | 16 (5.3) | 25 (8.3) |
| Anemia NOS | 15 (5.0) | 11 (3.7) |
| Hypokalemia | 14 (4.7) | 15 (5.0) |
| Oral candidiasis | 13 (4.3) | 10 (3.3) |
| Leukopenia NOS | 11 (3.7) | 13 (4.3) |
| Cough | 11 (3.7) | 4 (1.3) |
| Anemia NOS aggravated | 10 (3.3) | 10 (3.3) |
| Lymphopenia | 10 (3.3) | 7 (2.3) |
| Liver function tests abnormal | 10 (3.3) | 4 (1.3) |
| Neutropenia | 9 (3.0) | 14 (4.7) |
| Constipation | 9 (3.0) | 10 (3.3) |
| Herpes simplex | 7 (2.3) | 12 (4.0) |
| Dizziness | 6 (2.0) | 13 (4.3) |
| Abdominal pain NOS | 5 (1.7) | 13 (4.3) |
| Aspartate aminotransferase increased | 4 (1.3) | 10 (3.3) |

Source: Adapted from NDA Study VER002-4 Table 37.

**Table 21: Overall Summary of Adverse Events in the Pivotal Esophageal Candidiasis Study**

| **Safety Parameter** | Treatment Arm, n (%) | |
|---|---|---|
| | **Anidulafungin IV 100/50 mg N= 300** | **Fluconazole PO 100 mg N= 301** |
| Number of patients with at least one AE | 237 (79.0) | 226 (75.1) |
| Number of patients with at least one related adverse event | 28 (9.3) | 36 (12.0) |
| Patients with at least one adverse event leading to discontinuation | 29 (9.7) | 23 (7.6) |
| Number of patients with at least one severe intensity AE | 57 (19.0) | 39 (13.0) |
| Number of patients with at least one life-threatening AE | 16 (5.3) | 22 (7.3) |
| Sudden death | 1 (0.3) | 2 (0.7) |

The adverse event rates by treatment arm for life-threatening and severe intensity adverse events are provided in Table 22. A summary table of drug-related adverse events by treatment group is provided in Table 23.

**Table 22: Life-Threatening and Severe Intensity Adverse Events Occurring in ≥ 2 Patients Overall**

| Preferred Term | Treatment Arm, n (%) | |
|---|---|---|
| | **Anidulafungin IV 100/50 mg QD N= 300** | **Fluconazole PO 100 mg QD N= 301** |
| **Life-threatening** | | |
| Number of patients with at least one life-threatening AE | 16 (5.3) | 22 (7.3) |
| Cachexia | 2 (0.7) | 0 |
| Sepsis NOS | 1 (0.3) | 1 (0.3) |
| Toxoplasmosis NOS | 1 (0.3) | 1 (0.3) |
| Inappropriate antidiuretic hormone secretion | 0 | 2 (0.7) |
| Sudden death | 1 (0.3) | 2 (0.7) |
| **Severe** | | |
| Number of patients with at least one severe intensity AE | 57 (19.0) | 39 (13.0) |
| Lymphopenia | 3 (1.0) | 3 (1.0) |
| Dyspnea exacerbated | 3 (1.0) | 0 |
| Pyrexia | 3 (1.0) | 0 |
| Dehydration | 2 (0.7) | 3 (1.0) |
| Hyponatremia | 2 (0.7) | 1 (0.3) |
| Asthma aggravated | 2 (0.7) | 0 |
| Cholecystectomy | 2 (0.7) | 0 |
| Cryptococcosis | 2 (0.7) | 0 |
| Esophageal candidiasis | 2 (0.7) | 0 |
| Pneumonia bacterial NOS | 2 (0.7) | 0 |
| Anemia NOS aggravated | 1 (0.3) | 5 (1.7) |
| Aspartate aminotransferase increased | 1 (0.3) | 3 (1.0) |
| Disseminated tuberculosis | 1 (0.3) | 3 (1.0) |
| Anemia NOS | 1 (0.3) | 2 (0.7) |
| Diarrhea aggravated | 1 (0.3) | 2 (0.7) |
| Hypokalemia | 1 (0.3) | 2 (0.7) |
| Dyspepsia | 1 (0.3) | 1 (0.3) |
| Hemoglobin decreased | 1 (0.3) | 1 (0.3) |
| HIV infection NOS | 1 (0.3) | 1 (0.3) |
| Hyperglycemia NOS | 1 (0.3) | 1 (0.3) |
| Leukopenia NOS | 1 (0.3) | 1 (0.3) |
| Neutropenia | 1 (0.3) | 1 (0.3) |
| Pleural effusion | 1 (0.3) | 1 (0.3) |
| Pneumonia NOS | 1 (0.3) | 1 (0.3) |
| Delirium | 0 | 2 (0.7) |
| Herpes simplex | 0 | 2 (0.7) |

Source: Adapted from NDA Study VER002-4 Table 38

**Table 23: Related Adverse Events Occurring in ≥ 2 Patients in a Treatment Group**

| Preferred Term | Treatment Arm, n (%) | |
|---|---|---|
| | Anidulafungin IV 100/50 mg QD | Fluconazole PO 100 mg QD |
| | N= 300 | N= 301 |
| Number of patients with at least one related adverse event | 28 (9.3) | 36 (12.0) |
| Phlebitis NOS | 2 (0.7) | 4 (1.3) |
| Nausea | 2 (0.7) | 3 (1.0) |
| Headache NOS | 2 (0.7) | 2 (0.7) |
| Thrombocytopenia | 2 (0.7) | 2 (0.7) |
| Cough | 2 (0.7) | 1 (0.3) |
| Thrombophlebitis superficial | 2 (0.7) | 0 |
| Dyspepsia aggravated | 1 (0.3) | 3 (1.0) |
| Dyspepsia | 1 (0.3) | 2 (0.7) |
| Aspartate aminotransferase increased | 1 (0.3) | 2 (0.7) |
| Vomiting NOS | 1 (0.3) | 2 (0.7) |
| Pyrexia | 0 | 3 (1.0) |
| Pancytopenia | 0 | 2 (1.0) |
| Hypokalemia | 0 | 2 (0.7) |

Source: NDA Study VER002-4 Table 39

**Safety Summary**

In summary, the human safety database for anidulafungin comprises data from 461 subjects from the Phase 2 and 3 studies in the clinical development program, including 300 patients from the pivotal Phase 3 study. The number of subjects that have received anidulafungin intravenously at doses of 100/50 mg for durations of 10 or more days is 412. Of these 412 subjects, 331 received at least 14 days of IV anidulafungin. In general, the rates of adverse event reported for anidulafungin treated patients in the single pivotal Phase 3 study was similar to the control drug, fluconazole. Preclinical and clinical data did not reveal a signal or evidence of QT prolongation.

Several acute and/or repeated-dose animal studies identified the liver as a target organ of toxicity as shown by slight to moderate hepatopathy with related elevations in ALT and AST levels. An apparent dose and duration-dependent response in elevations in AST, ALT was observed in study VER002-5 which examined higher doses of intravenous anidulafungin.

In the Phase 3 trial there were 23 deaths (7.7%) on anidulafungin and 20 deaths (6.6%) on fluconazole. One death (anidulafungin arm) was considered by the investigator to be possibly drug-related. This patient had a history of alcohol abuse, pulmonary tuberculosis, bronchiectasis, and right-sided heart failure. He was on 14 concomitant medications during or in the days preceding his enrollment in the anidulafungin EC study. He died on the — day of anidulafungin therapy. The investigator initially considered the death due to underlying pulmonary and cardiac conditions. No autopsy was performed. About 3 months later, the investigator revised the cause of death and considered that the jaundice and respiratory failure resulted from hepatic necrosis with multisystem failure, which could possibly be related to anidulafungin. A consult from the Office of Drug Safety concluded that despite the patients underlying medical conditions, that this event may possibly represent hepatotoxicity due to anidulafungin cannot be excluded.

## Appendix A. Outcomes for other Recent EC Trials for other Drugs approved for EC

Currently-Approved Treatments for Esophageal Candidiasis (EC)

- Diflucan (fluconazole) (tablets, oral suspension, and for IV injection)
- Sporanox (itraconazole) (oral solution)
- Vfend (voriconazole) (tablets, oral suspension, and for IV injection)
- Cancidas (caspofungin), an intravenous echinocandin antifungal agent.

The product labeling for the azole antifungal agents contains information on the potential for hepatic toxicity and for drug interactions.

The response rates in the clinical studies used for the approval of caspofungin and voriconazole cannot be directly compared with those in the current anidulafungin NDA given the differences in study populations, study designs, definitions of outcomes, endpoints, use of prophylactic antifungal therapy, and potential variation in use of antiretroviral therapy.

For Cancidas (caspofungin), the primary efficacy endpoint was the proportion of patients with a favorable combined response (symptoms and endoscopy) at the 5-7 days visit. The overall combined response included the assessment of symptoms and endoscopic lesions. A "favorable" response was defined as both complete symptomatic resolution and complete resolution of lesions or a 2-grade reduction from baseline scores.

For Vfend (voriconazole) the protocol defined primary efficacy endpoint was success defined as a normal endoscopy at EOT or at least a 1 grade improvement over baseline endoscopic score. The protocol for the voriconazole also included a follow-up visit 4 weeks post EOT that was based on symptomatic (rather than endoscopic) assessment.

The tables from the Clinical Studies Sections from the Labeling for Cancidas and Vfend for the indication of esophageal candidiasis are provided below

### Cancidas® (Caspofungin)

**Favorable Response Rates for Patients with Esophageal Candidiasis**

| | CANCIDAS | Fluconazole | % Difference * (95% CI) |
|---|---|---|---|
| Day 5-7 post-treatment | 66/81 (81.5%) | 80/94 (85.1%) | -3.6 (-14.7, 7.5) |
| *calculated as CANCIDAS - fluconazole | | | |

**Relapse Rates at 14 and 28 Days Post-Therapy in Patients with Esophageal Candidiasis at Baseline**

| | **CANCIDAS** | **Fluconazole** | **% Difference *(95% CI)** |
|---|---|---|---|
| Day 14 post-treatment | 7/66 (10.6%) | 6/76 (7.9%) | 2.7 (-6.9, 12.3) |
| Day 28 post-treatment | 18/64 (28.1%) | 12/72 (16.7%) | 11.5 (-2.5, 25.4) |
| *calculated as CANCIDAS – fluconazole | | | |

## Vfend® (Voriconazole)

**Success Rates In Patients Treated for Esophageal Candidiasis**

| Population | Voriconazole | Fluconazole | Difference % (95% CI)[a] |
|---|---|---|---|
| Per Protocol | 113/115 (98.2%) | 134/141 (95.0%) | 3.2 (-1.1, 7.5) |
| Intention-to-Treat | 175/200 (87.5%) | 171/191 (89.5%) | -2.0 (-8.3, 4.3) |

a CI confidence interval of the difference (Voriconazole – Fluconazole) in success rates.

**Clinical and Mycologic Outcome by Baseline Pathogen in Patients with Esophageal Candidiasis**

| Pathogen[a] | Voriconazole | | Fluconazole | |
|---|---|---|---|---|
| | Favorable Endoscopic Response[b] | Mycologic Eradication[b] | Favorable Endoscopic Response[b] | Mycologic Eradication[b] |
| | Success/Total (%) | Eradication/Total (%) | Success/Total (%) | Eradication/Total (%) |
| *C. albicans* | 134/140 (96) | 90/107 (84) | 147/156 (94) | 91/115 (79 |
| *C. glabrata* | 8/8 (100) | 4/7 (57) | 4/4 (100) | 1/4 (25) |
| *C. krusei* | 1/1 | 1/1 | 2/2 (100) | 0/0 |

[a] Some patients had more than one species isolated at baseline
[b] Patients with endoscopic and/or mycological assessment at end of therapy

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/s/
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Edward Cox
5/21/04 11:52:16 AM
MEDICAL OFFICER

Renata Albrecht
5/21/04 12:06:30 PM
MEDICAL OFFICER

# Teleconference Minutes

**Teleconference Date:** April 19, 2004

**Application Numbers:** NDA 21-632: Anidulafungin (VER002) for Injection

**Sponsor:** Vicuron Pharmaceuticals, Inc.

**Attendees:**

**Vicuron Pharmaceuticals**

Tim Henkel, M.D., Ph.D.; Executive VP & Chief Medical Officer
David Krause, M.D.; Senior VP, Clinical Research & Medical Affairs
Marty Stogniew, Ph.D.; Senior VP, Nonclinical Development
Harriette Nadler, Ph.D.; Senior Director, Regulatory Affairs & Compliance

**FDA- Division of Special Pathogen and Immunologic Drug Products**

Ed Cox, M.D., M.P.H.; Office of Drug Evaluation IV Acting Director
Renata Albrecht, M.D.; Division Director
Marc Cavaille-Coll, MD, Ph.D.; Medical Officer Team Leader
Ekopimo Ibia, MD, MPH; Medical Officer
Kristen Miller, Pharm.D.; Regulatory Project Manager

## Background

Vicuron submitted a NDA for anidulafungin in April 2003. On January 14, 2004, Vicuron was notified that the PDUFA goal date for NDA 21-632 would be extended by three months, to May 25, 2004 due to submission of a major amendment in the last three months of the review cycle. During the week of March 29, 2004, the Division requested a brief teleconference to update the sponsor on the review status, and to answer any questions.

## Discussion

Following introductions, the Division explained that all outstanding consults have been received and reviews completed and that an action is anticipated in two to three weeks. Vicuron was then asked to provide some detail on their on going studies.

1. *The phase I drug interaction with voriconazole study is a three arm crossover design. This study has shown that there is no impact on the pharmacokinetics of either medication.*
2. *The uncontrolled, open label study in fluconazole refractory mucosal candidiasis has currently enrolled 18 patients.*
3. *The last cohort of the pediatric study has been completed.*
4. *The phase 3 study of invasive candidiasis has enrolled 160 patients. They expect the final study report to be submitted by early 2005.*

*Vicuron asked if there are any PK or toxicology questions anticipated, as many Vicuron employees will be out of the country until May 5, 2004 (although Dr. Nadler will be in the office).* The Division replied that there does not appear to be any, but if anything arises, Dr. Miller will be in contact with Dr. Nadler.

**Action Items**

1. The Division will provide an update on the review status to Vicuron in approximately two weeks.

Minutes Preparer: Kristen Miller, PharmD; Project Manager
Concur: Ed Cox, M.D., M.P.H.; Acting Director, Office of Drug Evaluation IV

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/s/
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Kristen Miller
5/18/04 04:02:20 PM
CSO

Edward Cox
5/18/04 06:23:36 PM
MEDICAL OFFICER

# Memorandum

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

DATE: 25 March 2004

FROM: John R. Senior, M.D., Associate Director for Science, Office of Pharmaco-epidemiology and Statistical Science (OPSS), HFD-030

TO: Renata Albrecht, M.D., Director, Division of Special Pathogen and Immunologic Drug Products (DSPIDP), HFD-590
Ekopimo O. Ibia, M.D., Medical Reviewer, HFD-590

VIA: Mark Avigan, M.D., Director, Division of Drug Risk Evaluation, HFD-400, Office of Drug Safety (ODS)
Paul Seligman, M.D., Director, (OPSS), HFD-030

SUBJECT: ODS consultation #D040163 regarding hepatotoxicity possibly induced by use of anidulafungin for treatment of esophageal candidiasis

Documents reviewed:

1) Consultation request from HFD-590 to ODS/DDRE dated 11 March 2004, assigned #D040163 for desired completion date of 25 March 2004
2) E-mail request dated 25 February 2004 from Dr. Ekopimo Ibia
3) Package of material from Vicuron Pharmaceuticals sent 5 March 2004 providing information about patient 13-008 reported in application for New Drug Application (NDA) 21-632
4) Medical literature (PubMed) on antifungal toxicity
5) DSS and DFS listings for reviews submitted up to 24 March 2004 for anidulafungin, N 021632
6) ODS consultation #D040090 by Safety Evaluator Sarah J. Singer sent 18 March 2004

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Dr. Ibia asked on 25 February 2004 that we review and evaluate a case of rapid, fatal hepatic failure occurring in a patient who had received three days dosing with anidulafungin for treating Candida infection of his esophagus. The patient was a 53-year-old man who had a long history of pulmonary tuberculosis, bronchiectasis, cor pulmonale, and right heart failure. He was currently on treatment with oral corticosteroids, bronchodilators, and antibiotics. He had been chronically ill with cough productive of yellow sputum, with wheezing and shortness of breath, dysphagia, constipation, abdominal discomfort, weight loss, dysuria, and backache. He appeared cachectic on [ ] when he was seen as an outpatient for assessment of esophageal candidiasis. Examination at that time showed that he was afebrile (oral temperature 35.9° C.), tachypneic at 32/minute, pulse 100/minute, blood pressure 107/80 mmHg. He had rhonchi and coarse crepitations in both lungs, especially lower left anteriorly, a left parasternal systolic murmur, palpable liver, jugular venous distention, and 3+ leg edema. A recent chest x-ray showed diffuse bronchiectasis with bilateral severe lung damage. Electrocardiogram showed normal left- sided measurements but right atrial and ventricular enlargement and cor pulmonale. The hepatic veins and inferior vena cava were said to be congested, but the screening liver tests done on [ ] showed serum activities of enzymes (alanine aminotransferase, ALT; aspartate aminotransferase, AST; alkaline phosphatase, ALP;

gamma-glutamyltransferase, GGT) all in the normal range. But on [ ] the ALT had been 100 U/L. He was started on anidulafungin on [ ], transferred to a regional hospital, but appeared improved the next day and was sent home. On [ ] his dyspnea increased, with tachypnea and cough, dysphagia, abdominal pain, and appearance of scleral icterus. Repeat blood tests were drawn for ALT and GGT, and for serum total bilirubin and creatine phosphokinase (CPK), but he died that day, [ ] before results became available. On [ ] the results for three days before were ALT 4168, GGT 72, CPK 216 U/L, and total bilirubin (TBL) 100 µ/L. Neither autopsy nor liver biopsy were obtained. The investigator diagnosed "hepatic necrosis with multi-system failure resulting in death," and felt that it was possibly related to treatment with anidulafungin.

*Comment: This case description is as provided by the sponsor in Attachment 6 for the VER002-4 Clinical Study Report, a copy of which was in the material resubmitted on 5 March 2004. It is obviously not carefully done (mixup up in dates of tests done in [ ] when he died in [ ] no range of normal values ; dose of anidulafungin not given; implications of histological findings without tissue being taken, and inadequate clinical synthesis of the data). The death was rapid, rather than a slow respiratory death, and even rather fast for acute liver failure, suggesting arrhythmic death associated with severe acidosis, in the absence of sufficient data to be sure. We requested addition al information about the case from the sponsor.*

Ms Sarah Singer, responding to a request 18 February 2004 for and ODS safety evaluation, replied on 18 March (ODS #D040090). She found no cases of anidulafungin-associated hepatotoxicity, but did a search for another echinocandin antifungal agent, caspofungin, that had been approved on 26 January 2001 (as CANCIDAS, Merck) for treatment of invasive aspergillosis in patients refractory to or intolerant of other therapies. There were 8 cases of caspofungin-associated hepatotoxicity that also were confounded by a multiplicity of drugs so that the causal role of one is difficult to prove, but that also were characterized by rapid onset of hepatotoxicity markers shortly after starting the antifungal treatment. She summarized the 8 cases, 4 from the United States and 1 each from the United Arab Emirates, Austria, Germany, and Switzerland. The labeling for CANCIDAS contains mention of jaundice and increased serum enzymes and bilirubin, but at lower incidence than for a comparator antifungal drug, amphotericin B. She also carried out searches of the Adverse Event Reporting System (AERS) for hepatotoxicity of other 6 drugs also started on [ ], the same day anidulafungin was started in him: LENTOGESIC (contains acetaminophen), prednisone, ATROVENT, BECLATE, GAVISCON, prochlorperazine. None of them are considered likely to have caused such rapid and overwhelming liver failure. Of the drugs that he had taken previously that might be associated with liver failure, ciprofloxacin had been stopped on [ ], and he had been taking omeprazole long-term without difficulty. She pointed out that all antifungal agents currently approved in the United States for treatment of systemic mycoses are associated with significant toxicities. Writing for ODS, she recommended that if anidulafungin is approved for treatment of candidal infections, labeling should state that a case a fatal acute liver failure was seen during clinical trials, and that the drug could not be excluded as a potential cause, despite the complicating factor of concurrent right heart failure.

*Comment: The finding of significant but rare hepatotoxicty associated with caspofungin, a recently approved member of this new class of echinocandin agents, is of great interest and possible direct pertinence. Caspofungin is a large, complex, semisynthetic molecule (Merck Index 1899) that has*

*its effect on inhibition of 1,3-β-D-glucan synthase required for fungal cell wall synthesis, the same mechanism of action proposed for anidulafungin by the sponsor (chemistry review not available and not found in the Document File System, DFS, on 24 March 2004). The new class of echinocandins (caspofungin, anidulafungin, micafungin) all have a central, large, cyclic hexapeptide nucleus with N-terminal linoleoyl and an amino group connecting the 3-hydroxy-4-methylproline moiety to the δ-amino group of dihydroxyornithine to form the ring. The three new drug agents differ only in their patterns of hydroxylations. (Wiederhold and Lewis, 2003). The agents were developed to be safer than earlier antifungal agents that caused collateral damage to host cells (amphotericin B) and drug interactions (the –conazoles). Caspofungin was the first approved, as CANCIDAS, Merck for treatment of invasive aspergillosis in January 2001. Anidulafungin was also under development [redacted] by Eli Lilly, but was discontinued because of poor oral bioavailability. Versicor in 1999 obtained rights to its development, then merged with Biosearch of Milan to form Vicuron, the current sponsor of NDA 21-632 (Drugs in R&D, 2003). It is of interest that although 8 cases of caspofungin hepatotoxicity have been reported to AERS, only one case is even mentioned in the published literature, in an acute leukemic patient who had moderate but reversible hepatotoxicity (Aliff, et al., 2003).*

In the supplemental information sent by Vicuron on 5 March 2004, it is stated that no other patient out of 791 who received anidulafungin in 20 clinical studies reported to the NDA, or in 114 other on-going studies since the last IND report of October 2002. An additional three pages of narrative information about the case, normal ranges for the laboratory data, and a two-page summary of a consultation with Dr. [redacted] hepatologist [redacted] The three pages of narrative amplify but do not change the story. More detail about other drug doses and times of administrations were provided. The medical monitor for the contract research organization managing the study discussed the possible causal attribution with the investigator, and revision of the cause of death was made "probable systemic inflammatory response syndrome, SIRS." On [redacted] when the investigator learned of the sharp rise in ALT, AST, and bilirubin, he made possible attribution of those changes to study drug, but the cause of death as "cardio-respiratory," and not the study drug. He also mentioned that the general metabolic disturbance could have contributed to a serious arrhythmia. On March 2002, the study was unblinded and the study drug was thought to be *fluconazole*, which led the investigator again to revise on [redacted] his cause of death to "severe hepatic necrosis with multi-system organ failure," due to fluconazole, "known to be a hepatotoxic drug," and not SIRS. On [redacted] it was discovered by the sponsor that the study drug was not fluconazole but anidulafungin.

On review of the more complete information, Dr.[redacted] who expressed his opinion that hepatic congestion secondary to right heart failure put the patient at risk for ischemic "shock" liver, but thought the death not typical of liver failure and more likely a cardiac arrthymia. This he postulated may have followed concurrent use of theophylline and ciprofloxacin in which the latter led to high levels of the former by metabolic competition. After further consultations, the sponsor postulated that perhaps a pulmonary embolism, arrhythmia, or hypotensive episode caused ischemic hepatic injury, and invoked some of the other drugs the patient received. These included LENTOGESIC ( a combination of pemoline [CYLERT] 2.5 mg and acetaminophen 400 mg), and it was stated that both of them, in sufficient amount, may cause liver injury. Finally, the supplemental material contained the full labeling for CYLERT and CIPRO (ciprofloxacin).

***Comment: The sponsor has sought a variety of alternative explanations for the possibility that their experimental echinocandin agent anidulafungin may have played a role in the fulminant liver injury and death of this patient. The shifting opinions of the investigator do not reassure us that the various attributions of what caused what are accurate. Not to say this is not an easy case to resolve, and there were many confounding factors, as is often the situation It remains true that the patient was chronically ill, was on many medications, and had significant right heart failure that very likely produced centrilobular congestion in the liver and consequent hypoxia at that site. Whether he had an arrthymia, or a pulmonary embolus, or a hypotensive episode, can only be speculated upon. It is entirely possible that a combination of effects produced the acute hepatic failure, with drug toxicity superimposed on impaired liver function from passive congestion. The sudden death suggests final cardiac arrest rather than either liver or respiratory failure. The timing of the events very strongly suggests that taking anidulafungin did something adverse and very bad to this patient. We cannot talk about liver necrosis, for that is a pathologic diagnosis requiring that liver tissue be examined, which was not done. It remains quite likely that this case represents possible hepatotoxicity of anidulafungin.***

Recommendations:

1. This case cannot be dismissed. It must be included in the labeling [ ]
2. Other cases must be looked for in patients treated with this drug. Systemic fungal diseases often occur in otherwise very sick patients who are on other therapies and have underlying problems, which may make them more vulnerable to or less able to recover from additional liver injury caused by anidulafungin.
3. Other agents in this class should be watched carefully as well (caspofingin, micafungin), and full reports of hepatotoxicity, even if relatively rare, be studied thoroughly.

John R. Senior, M.D.

cc: ODS PID#D040163
M. Avigan, ODS/DDRE
P. Seligman, OPSS
P. Guinn, DDRE
S. Singer, DDRE
R. Albrecht, HFD-590
E. Ibia, HFD-590
K. Miller, HFD-590

## References

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/s/
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John Senior
4/6/04 12:41:00 PM
MEDICAL OFFICER
Minor changes made 6 April to document submitted 25 March 2004 (see e-mail note)

| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION<br>CENTER FOR DRUG EVALUATION AND RESEARCH | ODS POSTMARKETING SAFETY REVIEW | ODS PID#, DATE:<br>D040090<br>March 18, 2004 |
|---|---|---|

| TO: | FROM: |
|---|---|
| Renata Albrecht, M.D., Director<br>Division of Special Pathogen and Immunologic Drug Products (DSPIDP), HFD-590 | Sarah J. Singer, R.Ph., Safety Evaluator<br>Division of Drug Risk Evaluation (DDRE), HFD-430 |

| DESIRED COMPLETION DATE:<br>March 12, 2004 | REQUESTOR:<br>Kristen Miller, Pharm.D., Regulatory Project Manager |
|---|---|
| DATE RECEIVED BY ODS:<br>February 18, 2004 | |

| DRUG: | NDA #: | SPONSOR: |
|---|---|---|
| Anidulafungin | 21-632 | Vicuron Pharmaceuticals |

**EVENT:**
Potential hepatic toxicity

**EXECUTIVE SUMMARY:**

After receiving notification that a patient participating in an anidulafungin trial experienced fatal fulminant hepatitis three days after starting the drug, DSPIDP asked DDRE if any of the patient's concomitant medications or caspofungin (another echinocandin antifungal) has been associated with acute fulminant hepatic failure.

AERS was searched for all cases of liver failure/liver necrosis/fulminant hepatitis associated with caspofungin, and for cases of liver failure/fulminant hepatitis associated with the six drugs started the same day as anidulafungin. Since the trial patient's liver function tests (LFTs) had been within normal limits shortly before anidulafungin was started, it was deemed unlikely that any of his longer-term medications would have been the cause of his rapid-onset acute liver failure.

AERS provides very little evidence that the six concomitant drugs would have been likely to have caused his fulminant hepatitis. The only concomitant drug with a known hepatotoxic potential which might have been responsible would have been the acetaminophen component of Lentogesic, if given in an overdose situation or with alcohol (neither of which were mentioned in the case summary).

The eight AERS cases of caspofungin-associated hepatotoxicity are similar to the anidulafungin case in that they are quite complex and the causal role of the drug is difficult to assess. However, they also share the similarity that LFTs increased quite abruptly within days of starting a course of the echinocandin in four of the caspofungin cases and the anidulafungin case. Although the evidence is not overwhelming, it suggests that there is a possibility the trial patient's newly-introduced echinocandin therapy may have been responsible for his sudden dramatic increase in LFTs and eventual death due to fulminant hepatitis.

The antifungal agents currently approved in the United States for use in systemic mycoses are all associated with significant toxicities. Each clinician should choose the most appropriate drug for a given patient based on a risk/benefit analysis that takes into account the morbidity/mortality of the condition being treated as well as the known adverse event profiles of the possible treatment choices. **ODS recommends** [illegible]

**REASON FOR REQUEST/REVIEW:**
A patient participating in an anidulafungin trial died of hepatic necrosis with multiorgan failure three days after starting the drug. He was receiving 13 concomitant medications. DSPIDP asked DDRE if any of those medications has been reported to cause acute fulminant hepatic failure. In addition, they asked if ODS has received any reports of fulminant hepatitis associated with caspofungin, which is structurally related to anidulafungin and is the only member of the echinocandin class of antifungals approved in the United States.

**ADDITIONAL INFORMATION ON THE ANIDULAFUNGIN CASE:**
DDRE contacted Dr. Ekopimo Ibia of HFD-590 for additional information on the case which prompted the consult request.

The patient was a 53-year-old male with a history of cor pulmonale, right congestive heart failure, tuberculosis, and bronchiectasis. He received anidulafungin for esophageal candidiasis. Three days before initiation of anidulafungin his screening liver function tests (LFTs) were all within normal limits: ALT 16 U/L, AST 16 U/L, alkaline phosphatase 76 U/L, and GGT 52 U/L. (However, ALT had been 100 U/L 12 days earlier.) Blood results available after death showed a markedly elevated ALT of 4168 U/L with a GGT only somewhat higher than previously (72 U/L).

Of the 13 concomitant medications listed on the original consult request, only 6 were started the same day as anidulafungin: Lentogesic, prednisone, Atrovent, Beclate, Gaviscon, and prochlorperazine. Ciprofloxacin (labeled for fatal hepatic necrosis) had been discontinued 17 days prior to the start of anidulafungin. The start dates of the remaining drugs were unknown to the investigators, implying that they were long-term medications. (One of the drugs was omeprazole, labeled for fatal hepatic failure/necrosis.) Since the patient's LFTs were normal before starting anidulafungin, it is unlikely that any of those drugs would have been the cause of his acute hepatic failure.

This consult therefore will discuss only caspofungin and the six drugs started at the same time as anidulafungin[1].



[1] DDRE hepatologist Dr. Mark Avigan indicates that worsening right heart failure can cause hepatic necrosis. The possibility that the patient's right heart failure was the cause of his fulminant hepatitis cannot be ruled out and is a confounding factor in trying to determine drug attributability in this case.

**CASPOFUNGIN:**

The labeling for Cancidas® (caspofungin) lists jaundice and increased ALT, AST, alkaline phosphatase and bilirubin (direct and total) as having been reported in clinical trials, but at incidence rates much lower than were reported for the comparator drug, amphotericin B. The labeling also indicates that "rare cases of clinically significant hepatic dysfunction" have been reported postmarketing.

AERS was searched 2/23/04 for any case with caspofungin (Cancidas®) listed as a suspect drug and coded with a term appearing in an ODS list of MedDRA terms related to liver failure/necrosis. The list contains the following MedDRA terms: HEPATIC FAILURE AND ASSOCIATED DISORDERS (High-Level Term); HEPATIC NECROSIS (Preferred Term); HEPATITIS FULMINANT (Preferred Term); and LIVER TRANSPLANT (Preferred Term).

The search identified 8 unduplicated cases, of which the most relevant aspects are presented below. (Note: No units were provided for the LFTs on any of the reports.)

The cases are all very complex and most of the patients were receiving other drugs associated with hepatotoxicity, making it difficult to determine the role of caspofungin in the development of hepatic failure/necrosis. There is, however, a temporal relationship between the start of a course of caspofungin therapy and the development of LFT abnormalities (with or without clinically-manifest liver dysfunction) in cases #1, 2, 3, and 5.

1. AERS #3845471-4 (United States): A 58-year-old male with acute myelogenous leukemia was treated with caspofungin for an unspecified pulmonary fungal infection. One month earlier his hepatitis serologies had been negative for hepatitis A antibody, hepatitis B surface antibody, hepatitis B core IgM, and hepatitis C antibody. During 3 weeks of caspofungin treatment his alkaline phosphatase varied from 73 to 78 but his ALT, AST, and total bilirubin were stated to be within normal limits. He was discharged and switched to itraconazole. (The itraconazole labeling includes a bolded warning about serious hepatotoxicity including liver failure and death.) He was treated with a 2nd course of caspofungin upon readmission, following which his ALT was 97, AST 41; no LFT values are provided for the period following itraconazole but before caspofungin was restarted. Five weeks later he was treated with one day of gemtuzumab ozogamicin (Mylotarg®; labeling contains a boxed warning about hepatotoxicity). Caspofungin was restarted one week later. LFTs that day were: AST 54, ALT 58, alk phos 76, tbili 0.7. In less than 3 days his LFTs rose to AST 2410, ALT 1555, alk phos 82, tbili 2.5. The patient's renal function also declined (creatinine 2.1, BUN 57). Caspofungin was discontinued. The patient was now positive for hepatitis A antibody but his other serologies were still negative. He developed epistaxis, encephalopathy, and respiratory failure and died that day. His physician thought his hepatic failure could have been due to sepsis (blood cultures could not be performed) or Mylotarg® and considered caspofungin an unlikely etiology. He indicated, however, that the hepatic failure "did not follow the usual pattern for hepatotoxicity" from gemtuzumab.

2. AERS #3794347-X (United States): A 13-year-old female with a 3-year history of acute lymphocytic leukemia developed neutropenic fever following chemotherapy. Caspofungin was added to the Ambisome® which she had received for months. Her total bilirubin then rose to 14 although her other LFTs were not extremely high (AST 23, ALT 52, alk phos 122, GGT 48); she also had low (unspecified) albumin, an ammonia level of 83, and an INR of 1.7. Caspofungin was held a few days but her LFTs didn't change, so it was restarted at a lower dose. The patient also appeared septic and was started on several antibiotics; not all of the antibiotics were specified, but ciprofloxacin was among them. She then developed coagulopathy and encephalopathy, and caspofungin was discontinued again. She expired of a possible pulmonary embolism. Her physician stated that the role of caspofungin in the events was difficult to assess. The patient's LFTs with the exception of bilirubin were never very high. She had an abdominal ultrasound two days before her death which did not show any abnormalities. Although she appeared septic, blood cultures were always negative and she never needed pressors.

3. AERS #3959162-2 (United States): A 63-year-old female had been hospitalized for months following a double lung transplant when she was started on caspofungin for *Candida parapsilopsis*. She then developed an alkaline phosphatase of 796 although her other LFTs were not extremely high: AST 63, ALT 74, tbili 1.8. Caspofungin was discontinued but her alkaline phosphatase remained somewhat elevated (around 180). Her candidiasis recurred so she was restarted on caspofungin, but in one day her alkaline phosphatase rose to 1244 and her GGT to 2943 (other LFTs: AST 58, ALT 210, tbili 1.5). Caspofungin was discontinued and never restarted. The patient experienced numerous complications and remained hospitalized until her death two months later. An autopsy showed passive congestion of the liver with massive hepatic necrosis. Her physician indicated that she had been on multiple medications which could affect the liver, and also had evidence of adenoviral infection and a shock syndrome with probable shock liver. The physician used caspofungin extensively in other transplant patients and had seen no adverse reactions in those patients, so she did not think caspofungin was responsible this patient's hepatic necrosis.

**CASPOFUNGIN, cont'd.**

4. AERS #4010467-9 (Austria): A literature case: Voitl P, Scheibenpflug C, Weber T, Janata O, Rokitansky AM. Combined antifungal treatment of visceral mucormycosis with caspofungin and liposomal amphotericin B. Eur J Clin Microbiol Infect Dis **2002**;21:632-4. A previously healthy 17-year-old female developed necrotizing pancreatitis, followed by mold growth (with necrosis) on the liver and small bowel mucormycosis. Caspofungin was added to her liposomal amphotericin B; six days later ciprofloxacin, rifampin, and vancomycin were started. However, the patient deteriorated and developed hypotension followed by liver failure. She died of multiple organ failure 28 days after admission. The authors indicated that her antifungal treatment had been well-tolerated but unable to reduce the fungal burden. They apparently did not consider a possible drug etiology in the patient's liver failure.

5. AERS #4038731-8 (Germany): A 33-year-old male developed appendicitis followed by an adhesive ileus. During surgery his intestine was perforated and he later developed peritonitis, failure to anastomose, and sepsis. The day caspofungin was started for candidiasis, his alkaline phosphatase and GGT were elevated at 174 and 89, respectively; AST was 26 and ALT was 16. Over the next 5 days his LFTs increased to: alk phos 1909, GGT 1008, AST 681, and ALT 326. He was diagnosed with "hepatic insufficiency" and caspofungin was discontinued. [It should be noted that in Germany "hepatic insufficiency" may mean "hepatic failure"; however, the report does not indicate that the patient experienced any clinical manifestations of hepatic insufficiency such as jaundice, coagulopathy, or encephalopathy.] The patient's LFTs improved immediately and within 4 days were down to: alk phos 1052, GGT 192, AST 41, ALT 51. However, the next day alkaline phosphatase and GGT had increased again to 231 and 1678. Two weeks later he died of multiple organ failure, which was thought to be secondary to sepsis. The reporting physician thought that the patient's LFT abnormalities had possibly been related to caspofungin.

6. AERS #4190466-7 (United Arab Emirates): A 57-year-old male with multiple myeloma was started on caspofungin for skullbase aspergillosis. His LFTs just before starting caspofungin were all stated to be within normal limits except for GGT at 111 (normal range 9-40) and albumin at 31 (35-48). His only concomitant medication was thalidomide (labeled for hepatitis, liver enlargement and increased LFTs). Unspecified tests for hepatitis A, B, and C were negative. The report states that caspofungin was discontinued after three or four weeks because of liver failure, but gives no indication what led to the diagnosis. Three weeks after that the patient was hospitalized with edema, ascites, hepatomegaly, pleural and pericardial effusion, confusion, and "hepatic flap". LFTs at that time were: AST 59 (12-50), ALT 33 (8-65), GGT 112 (9-40), alk phos 247 (46-199), bili 30 (0-26), albumin 20 (35-48), ammonia 50 (>32), PT 22 (<15), and INR 1.8 (<1). The patient was treated only with "conservative treatment". He died 9 days after admission; causes of death were listed as acute liver failure, hepatic encephalopathy, multiple myeloma, and aspergillosis. No autopsy was performed. The reporter stated: "Clinical features of liver failure and biochemical evidence of sepsis and liver disease but LFTs not that striking. Note albumin low before casp and suggests some pre-existing liver disease. Association with casp is positive but as to direct cause we can only say possible".

7. AERS #4245414-8 (United States): The report states that a 32-year-old male had received a kidney-pancreas transplant. He was stated to have bone marrow aplasia. The report also states that he had hepatic graft-vs-host disease, with abnormal LFTs, although there is no mention of a bone marrow transplant. Caspofungin and antibiotics were administered for prophylaxis; the patient was stated to have been on fluconazole the month prior and to have had abnormal LFTs when caspofungin was started. He developed VRE bacteremia and was given linezolid and quinupristin/dalfopristin but he became septic and then developed heart, liver, and kidney failure. A liver biopsy was performed and showed cholestasis and GVHD, not drug toxicity. The patient died approximately one month after starting caspofungin. The reporter indicated that the multiorgan failure was not thought to have resulted from caspofungin toxicity "unless we consider failure of caspofungin as an adverse drug reaction".

8. AERS #4279551-9 (Switzerland): A patient of unstated sex and age received a bone marrow transplant and was later treated with caspofungin and voriconazole. (The labeling for voriconazole contains a warning about serious hepatic toxicity, including fulminant hepatic failure, seen in clinical trials.) On an unstated date, the patient developed liver failure and died. All other information is unknown at this time.

**LENTOGESIC:**

Lentogesic was one of the six concomitant drugs started on the same day as anidulafungin. It is a South African combination product. Online Martindale's indicates that it is available as two different formulations.

Both formulations contain acetaminophen, a well-known hepatotoxic drug at doses of >3 grams/day. Online Martindale's does not provide information on the amount of acetaminophen contained in Lentogesic.

The other ingredients in one formulation of Lentogesic are dextropropoxyphene, pemoline, and levoglutamide (glutamine).

The pemoline (Cylert®) labeling has a black-box warning about life-threatening hepatic failure, but it states that the earliest onset in the cases was 6 months after initiation of the drug. AERS was therefore searched for all cases of either hepatic failure or fulminant hepatitis reported after the labeling revision in 2000, to see if any of the recent reports had a rapid onset like the patient in the anidulofungin trial. There were six new cases. In one of them, symptoms (abdominal pain, pruritus, fatigue, and brown urine) appeared 2 to 3 weeks after starting pemoline, although the patient continued taking the drug for another 2 to 3 weeks before acute liver failure developed. Three of the six cases developed after lengthy treatment; no information on the time to onset was provided in two cases.

The (dextro)propoxyphene (Darvon®) labeling lists only abnormal liver function tests and jaundice, including cholestatic jaundice. AERS was searched for cases of either hepatic failure or fulminant hepatitis reported with propoxyphene. The search identified 23 cases, all of which were retrieved for hands-on analysis. All of them had one or more of the following confounding factors: co-administration of other drugs associated with hepatotoxicity; underlying liver disease; overdose (all of the overdose cases included overdoses of acetaminophen and/or multiple pain medications along with propoxyphene); too little information to make an assessment of the role of dextropropoxyphene.

The other ingredients in the other formulation of Lentogesic are promethazine and codeine.

The promethazine (Phenergan®) labeling does not mention liver events except for cholestatic jaundice. AERS was searched for cases of either hepatic failure or fulminant hepatitis reported with the drug; two cases were found. In one of the cases, the consultant hepatologist was convinced the patient's acute liver failure was due to the azithromycin he had started the same day as promethazine. The other case was poorly documented and did not provide the dates of administration of promethazine in relation to the advent of acute hepatic failure; it did state that the patient was also receiving Premarin®.

There thus does not appear to be much evidence from AERS that the ingredients in either version of Lentogesic (with the exception of acetaminophen if overdosed) would have been responsible for the patient's rapid-onset acute liver failure.

**PREDNISONE:**
The prednisone labeling is not provided in the PDR. However, the DrugDex Drug Evaluations entry for prednisone lists only "a few reports of corticosteroid-associated hepatomegaly" under the category Hepatotoxicity.

AERS was searched for cases of either liver failure or fulminant hepatitis associated with prednisone and reported since 1995, when the online imaging system became available. The search identified 44 cases, all of which were retrieved for hands-on analysis. All but 4 of the cases listed one or more of the following confounding factors: co-administration of other drugs associated with hepatotoxicity; liver failure arising subsequent to shock; viral hepatitis; hepatic graft-vs-host disease; hepatic neoplasm. One of the 4 cases described an 87-year-old patient who was inadvertently treated with 60 mg/day of prednisone for 2 months and developed renal, cardiac, and hepatic failure. The 3 other cases described patients receiving other drugs along with prednisone, but none of the concomitant medications is labeled for hepatotoxicity. The physician in one of the three cases speculated a viral etiology.

Given the extensive use of prednisone, these four cases of hepatic failure do not provide a compelling argument that the patient's prednisone was responsible for his rapid-onset acute liver failure.

**ATROVENT:**
Atrovent® (ipratropium) is not labeled for any hepatic events. AERS was searched for cases of hepatic failure or fulminant hepatitis with ipratropium listed as a suspect drug, but the search identified no cases.

**BECLATE:**
Beclate is a South African preparation of beclomethasone dipropionate. The labeling for the U.S. equivalent, Beclovent®, does not mention any hepatic events. AERS was searched for cases of hepatic failure or fulminant hepatitis with beclomethasone listed as a suspect drug. The search identified one Japanese case of fulminant hepatitis associated with the use of beclomethasone inhaler and seven other drugs; "the cause could not be identified". This case does not provide a compelling argument that the patient's beclomethasone was responsible for his rapid-onset acute liver failure.

**GAVISCON:**
AERS was searched using just the tradename Gaviscon® for cases of hepatic failure or fulminant hepatitis with Gaviscon® (aluminum hydroxide/magnesium carbonate) listed as a suspect drug, but the search identified no cases.

**PROCHLORPERAZINE:**
The prochlorperazine (Compazine®) labeling mentions only cholestatic jaundice and fatty changes in the liver. AERS was searched for cases of hepatic failure or fulminant hepatitis with prochlorperazine listed as a suspect drug. The search identified 3 cases, which were obtained for hands-on analysis. Two of the cases involved patients who had used prochlorperazine daily for years. The third patient died of renal and hepatic failure thought to be secondary to the sepsis which apparently predated prochlorperazine administration (she had a fever and DIC when the drug was started). These three cases thus do not provide a compelling argument that the patient's prochlorperazine was responsible for his rapid-onset acute liver failure

**CONCLUSIONS/RECOMMENDATION:**

AERS provides very little evidence that the six drugs started concomitantly with the trial patient's anidulafungin would have been likely to have caused his rapid-onset acute liver failure. The only concomitant drug with a known hepatotoxic potential which might have been responsible would have been the acetaminophen component of Lentogesic, if given in an overdose situation or with alcohol (neither of which were mentioned in the case summary).

The AERS cases of caspofungin-associated hepatotoxicity are similar to the anidulafungin case in that they are quite complex and the role of the drug is difficult to assess. However, they also share the similarity that LFTs increased quite abruptly within days of starting a course of the echinocandin in four of the caspofungin cases and the anidulafungin case. Although the evidence is not overwhelming, it suggests that there is a possibility the trial patient's newly-introduced echinocandin therapy may have been responsible for his sudden dramatic increase in LFTs and eventual death due to fulminant hepatitis.

The antifungal agents currently approved in the United States for use in systemic mycoses are all associated with significant toxicities. Each clinician should choose the most appropriate drug for a given patient based on a risk/benefit analysis that takes into account the morbidity/mortality of the condition being treated as well as the known adverse event profile of the possible treatment choices. **ODS recommends that**

| **REVIEWER'S SIGNATURE / DATE:** | **TEAM LEADER'S SIGNATURE / DATE:** |
|---|---|
| /S/ 3/8/04 | /S/ 3/12/04 |
| Sarah J. Singer, R.Ph. | Melissa M. Truffa, R.Ph. |
| **DIVISION DIRECTOR'S SIGNATURE / DATE:** | |
| /S/ 3/17/04 | |
| Mark Avigan, M.D., Director | |

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/s/

Sarah Singer
3/18/04 07:17:41 AM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
3/18/04 08:46:20 AM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Johann Viljoen, M.D.
56 Reid Street
Westdene, Bloemfontein 9300
SOUTH AFRICA

MAR - 8 2004

Dear Dr. Viljoen:

Between November 3 and 7, 2003, Ms. Linda Kuchenthal, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol # VER002-4 entitled: "A Phase 3 randomized, double-blind, double-dummy non-inferiority study of the safety and efficacy of intravenous anidulafungin (VER002) vs oral fluconazole in the treatment of patients with esophageal candidiasis") of the investigational drug anidulafungin, performed for Vicuron Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

We understand that you conducted this study under a U.S. Investigational New Drug Application (IND) subject to the U.S. Code of Federal Regulations (CFR), therefore, we are providing comments so that you will be aware of FDA's requirements for clinical trials conducted under an IND.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Kuchenthal during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI:
Field Classification: NAI
Headquarters Classification:
__x__1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
__x__inadequate informed consent form (03)
Deficiency Codes: 3

cc:
HFA-224
HFD-590 Doc.Rm. NDA#21-632
HFD-590 Review Div.Dir.
HFD-590 MO (Ibia)
HFD-590 PM (Miller)
HFD-47c/r/s/ GCP File #11081
HFD-47 GCP Reviewer (Storms)
HFR-SW350 DIB (Thorsky)
HFR-SW350 Bimo Monitor (Montgomery)
HFR-SW350 Field Investigator (Kuchenthal)
HFC-132
GCF-1 Seth Ray
r/d:KMS:1/23/04;2/6/04
reviewed:LKB:1/28/04
f/t:ml:2/9/04
o:**KMS\viljoenltr**

**Reviewer Note to Rev. Div. M.O.**

- This site screened 149 subjects, randomizing 113.
- There were 96 subjects that completed the study with 17 subjects that discontinued early. The early terminations were due to 8 subject's death; 3 subjects were lost to follow-up; 1 subject withdrew consent; and 5 subjects with SAEs that warranted early termination.
- All the case report forms for the 113 subjects were reviewed.
- All subjects received informed consent.
- Data generated from this site appear acceptable in support of the pending NDA.

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/s/
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Leslie Ball
3/8/04 07:01:11 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR - 8 2004

Christo Van Rensburg, M.D.
The Gastroenterology Unit
C7B, Room 151
Tygerberg Academic Hospital
Tygerberg, 7505
Cape Town, SOUTH AFRICA

Dear Dr. Van Rensburg:

Between November 10 and 14, 2003, Ms. Linda Kuchenthal, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol # VER002-4 entitled: "A Phase 3 randomized, double-blind, double-dummy non-inferiority study of the safety and efficacy of intravenous anidulafungin (VER002) vs oral fluconazole in the treatment of patients with esophageal candidiasis") of the investigational drug anidulafungin, performed for Vicuron Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

We understand that you conducted this study under a U.S. Investigational New Drug Application (IND) and thus was subject to the U.S. Code of Federal Regulations (CFR); therefore, we are providing our comments so that you will be aware of FDA's requirements for clinical trials conducted under an IND.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Kuchenthal during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Leslie Ball, M.D

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

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Headquarters Classification:
__x__1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-590 Doc.Rm. NDA#21-632
HFD-590 Review Div.Dir.
HFD-590 MO (Ibia)
HFD-590 PM (Miller)
HFD-47c/r/s/ GCP File #11092
HFD-47 GCP Reviewer (Storms)
HFR-SW350 DIB (Thorsky)
HFR-SW350 Bimo Monitor (Montgomery)
HFR-SW350 Field Investigator (Kuchenthal)
GCF-1 Seth Ray
HFC-132 Kadar
r/d:KMS:2/3/04; 2/6/04
reviewed:LKB: 2/3/04
f/t:ml:2/9/04
o:**\KMS\vanrensburgltr**

**Reviewer Note to Rev. Div. M.O.**

- Dr. Van Rensburg's site screened 356 potential subjects, randomizing 152. There were 134 subjects that completed the study with 18 subjects that discontinued early. The early terminations were due to 7 subject deaths; 4 subjects were lost to follow-up; 1 subject withdrew consent; 1 subject had medication stolen; 1 subject refused further treatment; and 4 subjects with SAEs that warranted early termination.
- All subjects received informed consent.
- Subjects 10020 and 10073 baseline endoscopy was different than what was reported on the data listing. Subject 10020 baseline endoscopy was Grade 3 however, the data listing shows Grade 2 and Subject 10073 baseline was Grade 2 however, the data listing shows Grade 1.
- Data generated from this site appear acceptable in support of the pending NDA.

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/s/

Leslie Ball
3/8/04 06:49:18 PM

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✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

6 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(4) Draft Labeling

46 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

3 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

# MEMORANDUM OF MEETING MINUTES

| | |
|---|---|
| **MEETING DATE:** | February 20, 2004 |
| **TIME:** | 1:00 PM |
| **APPLICATION:** | NDA 21-632 (Anidulafungin for Injection) |
| **TYPE OF MEETING:** | Regulatory Briefing |
| **MEETING CHAIR:** | John Jenkins, M.D.: Director, Office of New Drugs (OND) |
| **MEETING RECORDER:** | Kristen Miller, PharmD: Regulatory Project Manager |

**DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS (DSPIDP) (and co-locates) ATTENDEES, TITLES, AND OFFICE/DIVISION**

| | |
|---|---|
| Renata Albrecht, M.D. | Division Director |
| Marc Cavaille Coll, MD, Ph.D. | Medical Officer Team Leader |
| Ekopimo O Ibia, M.D., M.P.H. | Medical Officer |
| Karen M Higgins, Sc.D. | Statistician Team Leader |
| Cheryl A Dixon, Ph.D. | Statistician |
| Shukal Bala, Ph.D. | Microbiology Team Leader |
| Norman R. Schmuff, Ph.D. | Chemistry Team Leader |
| Owen McMaster, Ph.D. | Pharmacologist |
| Philip Colangelo, Pharm.D., Ph.D. | Team Leader, Clinical Pharmacology/Biopharmaceutics |
| Dakshina Chilukuri Ph.D. | Clinical Pharmacology/Biopharmaceutics Reviewer (OCPB III) |
| Yaning Wang, Ph.D. | Clinical Pharmacology/Biopharmaceutics Reviewer (OCPB III) |
| Elizabeth Oen | Pharmacy Intern |
| Kristen Miller, Pharm.D. | Regulatory Project Manager |

**ATTENDEES, TITLES, AND OFFICE/DIVISION**

| | |
|---|---|
| John Jenkins, M.D. | Director, Office of New Drugs (OND) |
| Leo Chan, R.Ph. | Project Management Officer for Antimicrobial Drug Development and Resistance Initiatives |
| Sara Goldkind, M.D. | Medical Officer, Office of Pediatric Therapeutics |
| Florence Houn, M.D. | Director, Office of Drug Evaluation (ODE) III |
| David Jacobson-Kram, Ph.D. | Director of Pharmacology/Toxicology, OND |
| Robert Meyer, M.D. | Director, ODE II |
| Joanne Rhoads, M.D. | Director, Division of Scientific Investigations (DSI) |
| Rigoberto Roca, M.D. | Deputy Director, Division of Anesthetic, Critical Care and Addiction Drug Products (DACADP) |
| David Roeder, M.S. | Associate Director for Regulatory Affairs |
| David Ross, M.D., Ph.D. | Medical Officer Team Leader, Division of Anti-Infective Drug Products (DAIDP) |
| Arzu Selen, Ph.D. | Deputy Division Director, Division of Pharmaceutical Evaluation (DPE) III |

| | |
|---|---|
| Solomon Sobel, M.D. | Associate Director of Medical Affairs, Office of Pharmaceutical Science (OPS) |
| Robert Temple, M.D. | Associate Director of Medical Policy, Office of Medical Policy |
| C.T. Viswanathan, M.D., Ph.D. | Associate Director for Bioequivalence, DSI |

**BACKGROUND:** Vicuron submitted NDA 21-632 for anidulafungin on April 25, 2003. It contains one Phase 3, adequate and well-controlled study that is a non-inferiority design with a dose of 100mg per day of comparator drug (fluconazole), with two Phase 2 dose-ranging studies (one in esophageal candidiasis and the other in primarily candidemia). In addition, preliminary data included five patients from an ongoing fluconazole refractory mucosal candidiasis study. During the July 29, 2002 Pre-NDA meeting, the Division agreed to accept one robust study and supporting data. In December 2002, Vicuron informed the Division of a systematic randomization error. Subsequently, a DSI audit discovered that some patients had both the active drug and the comparator detected in one or more of their samples collected for PK analysis (unrelated to the systematic randomization error). Finally, in the single, large Phase 3 study, the primary endpoint is met but the product is inferior to comparator at the two-week follow-up.

**MEETING OBJECTIVES:** The purpose of the Regulatory Briefing is to discuss whether the application contains substantial evidence of safety and efficacy given the results of the Phase 3 study and the DSI audit report. Specifically, the questions are:

1. The sponsor has developed a corrected treatment assignment code for patients that the sponsor determined were at risk for systematic misassigment of study drug and has found concordant serum drug levels in the subset of patients for whom testing was available. Do these efforts satisfactorily address the issue of "misassignment" of study drug in the pivotal study? In addition, does the finding of 30 patients with at least one sample containing both drugs (anidulafungin and fluconazole) and the fact that 54% of the patients did not have serum levels measured, change this conclusion?

2. The sponsor provides data from one Phase 3 study and two supportive Phase 2 studies. Are the data in the package sufficiently robust to provide substantial evidence of safety and efficacy anchored in the one large pivotal clinical study given the issues of outcome at the end of treatment as well as 2 weeks later, the timing of the primary endpoint assessment, the safety profile, the systematic "misassignment" of study medication resulting in a corrected medication assignment code, and the exclusion of Center 19?

**DISCUSSION POINTS:**

After Dr. Jenkins called the meeting to order, Dr. Albrecht provided a brief overview of why the Regulatory Briefing was requested. Three main issues will be addressed:
1. The efficacy of anidulafungin at two-week follow-up (secondary endpoint)
2. DSI's finding during its audit of the systemic randomization error
3. Hepatic safety information, including one patient with possible anidulafungin-related hepatic toxicity

Dr. Ibia and Dr. Viswanathan then presented their slides (see attachment). The following discussions took place during the presentation:

When the company informed you that they would have only one adequate and well-controlled study using the lowest approved dose of the comparator, what comments were provided? *The Division agreed to the proposal as it was the largest EC trial proposed, but informed the sponsor that the study would have to be robust given the reliance on only a Phase 3 study with supportive data from Phase 2.*

*Is there any hint that a larger dose would provide better results?* Whether an increased dose would have lead to a better relapse rate cannot be known because it was not tested, but the better fluconazole results, despite the same duration of treatment, suggest room for improvement, perhaps by a larger (more suppressive) dose.

Following the presentation, the panel and Division discussed the issues.

*Sites 10 and 19 have a total of 22 patients with both fluconazole and anidulafungin on board. DSI found that 11% of patients from pop-PK subprotocol had both fluconazole and anidulafungin and these patients were distributed across 8 of 20 sites involved in pop-PK sampling. How this occurred is not known. Additionally, 54% of the patients did not have their plasma sampled. DSI concluded that the finding of both drugs appears to be real, more than a casual contamination and suggests a systemic procedural issue. DSI maintains that there is no assurance that 54% of the subject data are free from randomization error. DSI is not confident that the data is reliable. A question that must be answered is, given DSI audit findings, can you rely on this database. Was an analysis completed using only the patients that are known (by PK analysis) to have only received one drug?* Yes, and all analyses find the same results: effective (non-inferior) at end of treatment (EOT) and inferior at two-week follow-up.

*Was it effective against resistant/refractory Candida species?* The anidulafungin MICs were low, but it is not possible to determine if they were susceptible or resistant based on in vitro findings. The methods for in vitro testing of antifungal drugs are not standardized. Anidulafungin was effective against a few fluconazole-resistant strains in animals, and 5 refractory patients. However, the number is very small to conclude effectiveness against resistant candidiasis

*Anidulafungin is clearly more effective than placebo, but you did not use a control group to know that. It is clear that compared to fluconazole, relapse rates were higher, an undesirable outcome that could reflect use of too low a dose. At present it seems hard to argue that anidulafungin is not inferior to the control. The Division needs to decide how important that is. Not also that a low dose of the control was used. Conceivably, the drug could be labeled for fluconazole failures.*

*Another factor is the risk of liver toxicity vs. the potential toxicities of other therapies. Although there is high relapse, this may be more desirable than more dangerous toxicities, especially if the EC is only mild.* When patients relapsed, they relapsed back to baseline or worse, significantly more often than patients on fluconazole. One possible explanation is the presence of oral candidiasis, which was not looked at in a systematic fashion. The one patient who died of hepatotoxicity was discussed and the case was considered confounded because of other components in the patient's medical history including congestive heart failure, prior history of tuberculosis and alcohol, and use of multiple other medications.

Based on analysis of the information provided by the sponsor and DSI, and multiple analyses of the study results, the Review Team feels comfortable with the database. *Anidulafungin is XXX effective. The Division must determine what the standard for approval in this case should be. The anti-microbial divisions almost always look at drugs compared to an active control, usually insisting that even modest inferiority be ruled out because the consequences of drug failure matter a lot. If the Division felt that it was critical to compare this medication to an active control, it must have felt that the comparative effect mattered. As a general matter, drugs can be approved when they are inferior to other drugs but we would not do this if the lesser effectiveness represented a risk. If the risk were small or non-existent, e.g., delay of improvement of a symptom, approval would be usual, perhaps with labeling pointing out inferiority, if well established. If there were a toxicity concern too, that would argue against approval of a less effective product, unless there were still safety advantages over alternatives. The hepatic toxicity issue must be addressed thoroughly. Every patient's labs should be examined to determine the number of patients that have high bilirubin and transaminases, but have normal alkaline phosphate.*

*One final issue to weigh is the slow down of antibiotic and antifungal development. The FDA must balance between setting standards so high that companies stop development, and becoming so lax as to spark safety concerns.*

*You may want to consider cardio-renal's example of issuing a non-approval or approvable, and providing a public hearing to gain community feedback.*

Thank you very much for your input and guidance.

**Minutes Preparer:** _____
Kristen Miller, Pharm.D., Regulatory Project Manager, DSPIDP

**Division Concurrence:** _____
Renata Albrecht, M.D., Division Director, DSPIDP

**Chair Concurrence:** _____
John Jenkins, M.D., Director, OND

**ATTACHMENTS:** Slides presented by DSPIDP and DSI

Drafted by: KEM: 2/20/04

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/s/

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John Jenkins
3/19/04 04:28:28 PM

# NDA REGULATORY FILING REVIEW
**(Including Memo of Filing Meeting)**

NDA # **21-632** Supplement # **N/A** SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: [ ] **(under review)**
Generic Name: **Anidulafungin**
Strengths: **50 mg**

Applicant: **Vicuron**

Date of Application: **April 25, 2003**
Date of Receipt: **April 25, 2003**
Date clock started after UN: **N/A**
Date of Filing Meeting: **June 5, 2003**
Filing Date: **June 24, 2003**
Action Goal Date (optional): **February 25, 2004** User Fee Goal Date: **February 25, 2004**

Indication(s) requested: **Esophageal Candidiasis**

Type of Application: Original (b)(1) NDA **X** Original (b)(2) NDA _____
(b)(1) Supplement _____ (b)(2) Supplement _____
[If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

NOTE: If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S **7030410 (Systemic antifungal)** P **N/A**
Resubmission after a withdrawal? **No** Resubmission after a refuse to file? **No**
Chemical Classification: (1,2,3 etc.) **1 (NME)**
Other (orphan, OTC, etc.) **N/A**

User Fee Status: Paid **X (but waiting for small business waiver reimbursement)**
Waived (e.g., small business, public health) **April 14, 2003**
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES NO
User Fee ID # **4514**
Clinical data? YES **X** NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES NO

If yes, explain: **N/A**

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)]? **N/A**

YES NO

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? **N/A** YES NO

- Does the submission contain an accurate comprehensive index? [YES] NO
- 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:
- If an electronic NDA, does it follow the Guidance? [YES] NO
  **If an electronic NDA, all certifications must be in paper and require a signature.**
  Which parts of the application were submitted in electronic format?

  **It was a completely electronic submission (with all certificates submitted in paper).**

  Additional comments:

- If in Common Technical Document format, does it follow the guidance? [N/A] YES NO
- Is it an electronic CTD? [N/A] YES NO
  **If an electronic CTD, all certifications must be in paper and require a signature.**
  Which parts of the application were submitted in electronic format?

  Additional comments:

- Patent information included with authorized signature? [YES] NO
- Exclusivity requested? YES, _____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 must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. 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 the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge . . . ."
- Financial Disclosure information included with authorized signature? [YES] NO
  **(Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)**

- Field Copy Certification (that it is a true copy of the CMC technical section)? [YES] NO

**Refer to 21 CFR 314.101(d) for Filing Requirements**

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

- Drug name/Applicant name correct in COMIS? [YES] NO
  If not, have the Document Room make the corrections.

- List referenced IND numbers: **54,597 and**

- End-of-Phase 2 Meeting(s)? Date: **January 31, 2002** NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date: **July 29, 2002** NO
  If yes, distribute minutes before filing meeting.

## Project Management

- Package insert consulted to DDMAC? [YES] NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? [YES] NO

- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support?
  [N/A] YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  [N/A] YES NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support?
  [N/A] YES NO

- Has DOTCDP been notified of the OTC switch application? [N/A] YES NO

## Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  [N/A] YES NO

## Chemistry

- Did applicant request categorical exclusion for environmental assessment? [YES] NO

If no, did applicant submit a complete environmental assessment? N/A YES NO
If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? [YES] NO
- If parenteral product, consulted to Microbiology Team (HFD-805)? [YES] NO

**If 505(b)(2) application, complete the following section: N/A**

- Name of listed drug(s) and NDA/ANDA #:
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].*

  ____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

  ____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES NO
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES NO
  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO
  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO
  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    YES, IND # _____ NO

    OR
    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES NO

ATTACHMENT

## MEMO OF FILING MEETING

DATE: June 5, 2003

BACKGROUND:
The original IND (54, 597) for anidulafungin was filed by Eli Lilly on November 20, 1997. On June 18, 1999, sponsorship was transferred to Versicor (now Vicuron). Although early nonclinical and clinical studies were conducted using an oral formulation (51,111), a low extent of bioavailability and variability led to the selection of the intravenous formulation for clinical development.

ATTENDEES:

| | |
|---|---|
| Mark Goldberger, M.D. | Office of Drug Evaluation IV (ODE IV) Director |
| Edward Cox, M.D. | ODE IV Deputy Director |
| Renata Albrecht, M.D. | Division Director |
| Marc Cavaille Coll, MD, Ph.D | Medical Officer Team Leader |
| Ekopimo Ibia, MD, MPH | Medical Officer |
| Cheryl Dixon, Ph.D. | Statistician |
| Karen Higgins, Sc.D. | Statistician Team Leader |
| Philip Colangelo, Ph.D | Clinical Pharmacology/Biopharmaceutics Team Leader |
| Dakshina Chilukuri, Ph.D. | Clinical Pharmacology/Biopharmaceutics |
| Shukal Bala, Ph.D. | Microbiologist |
| Lynn Steele-Moore | Microbiologist |
| Norman Schmuff, Ph.D. | Chemistry Team Leader |
| Mark Seggel, Ph.D. | Chemistry Reviewer |
| Kristen Miller, PharmD | Regulatory Project Manager |

ASSIGNED REVIEWERS:

| **Discipline** | **Reviewer** |
|---|---|
| Medical: | Ekopimo Ibia |
| Statistical: | Cheryl Dixon |
| Pharmacology: | Owen McMaster |
| Chemist: | Mark Seggel |
| Biopharmaceutical: | Dakshina Chilukuri |
| Microbiology, sterility: | James McVey |
| Microbiology, clinical (for antimicrobial products only): | Lynn Steele-Moore |
| DSI: | Karen Storms |
| Regulatory Project Manager: | Kristen Miller |
| Other Consults: | Shannon Benedetto- DDMAC<br>Sammie Beam- DMETS |

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

CLINICAL FILE __X__ REFUSE TO FILE ____

- Clinical site inspection needed: [YES] NO
- 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 FILE __X__ REFUSE TO FILE ____ N/A

STATISTICS FILE __X__ REFUSE TO FILE ____

BIOPHARMACEUTICS FILE __X__ REFUSE TO FILE ____

- Biopharm. inspection needed: YES [NO]

PHARMACOLOGY FILE __X__ REFUSE TO FILE ____

- GLP inspection needed: YES [NO]

CHEMISTRY FILE __X__ REFUSE TO FILE ____

- Establishment(s) ready for inspection? [YES] NO
- Microbiology [YES] NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

__X__ 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.

__X__ Filing issues to be communicated by Day 74.
**See letter signed on July 7, 2003.**

**ACTION ITEMS:**

1. Document filing issues conveyed to applicant by Day 74.

_____
Kristen Miller, Pharm.D., Regulatory Project Manager, HFD- 590

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/s/

Kristen Miller
2/18/04 02:32:07 PM
CSO

# Teleconference Minutes

**Teleconference Date:** January 14, 2004

**Application Numbers:** NDA 21-632: Anidulafungin (VER002) for Injection

**Sponsor:** Vicuron Pharmaceuticals, Inc.

**Attendees:**

**Vicuron Pharmaceuticals**

Tim Henkel, M.D., Ph.D.; Executive VP & Chief Medical Officer
David Krause, M.D.; Senior VP, Clinical Research & Medical Affairs
Marty Stogniew, Ph.D.; Senior VP, Nonclinical Development
Harriette Nadler, Ph.D.; Senior Director, Regulatory Affairs & Compliance
Mark Klinger; Senior Manager, Regulatory Affairs

**FDA- Division of Special Pathogen and Immunologic Drug Products**

Renata Albrecht, M.D.; Division Director
Marc Cavaille-Coll, MD, Ph.D.; Medical Officer Team Leader
Ekopimo Ibia, MD, MPH; Medical Officer
Elizabeth Oen; Pharmacy Intern
Kristen Miller, Pharm.D.; Regulatory Project Manager

## Background

Vicuron submitted a new NDA for anidulafungin in April 2003. Prior to the submission, the Division informed Vicuron that since there would only be one pivotal study, that study would have to be very robust. Also prior to submission, the sponsor had informed the Division of a systematic reversal of assigned drugs in about 70% of subjects in study VER002-4. At that time the sponsor had taken remedial actions that the Division considered adequate. However, during the review and as part of data audit by the Division of Scientific Investigations, it was discovered that some patients were on both the control and the active therapy. In December 2003, the Division asked Vicuron to assay all plasma samples for fluconazole to better understand the extent of dual drug levels in the study participants. On January 13, 2004, the Division requested a brief teleconference with Vicuron to update them on the review, the regulatory steps planned, and to answer any questions.

## Discussion

Following introductions, the Division thanked Vicuron for providing the fluconazole assay results on January 6, 2004, but explained that it was a major amendment submitted in the last three months of the review cycle and that more time would be needed to discuss the regulatory

effects of the information. Therefore, a letter will be sent extending the User Fee goal date by three months, to May 25, 2004. Although a Regulatory Briefing is scheduled for the end of February and time will be needed for Office level sign-off, the Division does not anticipate delaying the decision until the end of the three-month extension. Vicuron explained that because they are a small company they will need to make this public, and asked if the statement could be reviewed prior to the announcement. The Division agreed.

Vicuron asked if there would be an Advisory Committee and were told that one would not occur in this review cycle. The Division also informed Vicuron that the Regulatory Briefing, being internal, should be very helpful and that some information may be requested. Vicuron also asked when they should expect the usual flurry of questions. The Division stated that there might not be many questions outside of the reanalysis of the data without study Site 19. Vicuron stated that they have this analysis completed and that they will submit that data. The Division thanked Vicuron and reminded them that the goal date extension is a one-time extension. Vicuron thanked the Division for the early notification of the extension.

**Action Items**

1. Vicuron will submit their analysis of the data without study Site 19.

Minutes Preparer: Kristen Miller, PharmD; Project Manager
Concur: Renata Albrecht, M.D.; Division Director

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/s/
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Kristen Miller
1/29/04 10:46:46 AM
CSO

Renata Albrecht
1/29/04 03:58:44 PM
MEDICAL OFFICER

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** February 1, 2006
**APPLICATIONS:** NDA 21-632
NDA 21-948
**DRUG NAME:** Eraxis® (anidulafungin)
**TYPE OF MEETING:** Pre-Approval Safety Conference

**ATTENDEES:**

Renata Albrecht, M.D. Division Director [Division of Special Pathogen and Transplant Products (DSPTP)]
Rosemary Johann-Liang, M.D. Deputy Director [Office of Drug Safety (ODS)/Division of Drug Risk Evaluation (DDRE)]
Melissa Truffa, R.Ph., Safety Evaluator Team Leader (ODS/DDRE)
Evelyn Farinas, R.Ph, M.G.A., Safety Evaluator (ODS/DDRE)
Tina Tezky, Pharm.D., Safety Evaluator, [ODS/Division of Medication Errors and Technical Support (DMETS)]
Quynh Nguyen, Pharm.D. Regulatory Health Project Manager (ODS/DDRE)
Leonard Sacks, M.D. Medical Team Leader (DSPTP)
Elizabeth O'Shaughnessy, M.D., Medical Reviewer (DSPTP)
Cheryl Dixon, Ph.D., Statistics Reviewer (Division of Biometrics III)
William Taylor, Ph.D. Pharmacology Toxicology Team Leader (DSPTP)
Owen McMaster, Ph.D. Pharmacology Toxicology Reviewer (DSPTP)
Mark Seggel, Ph.D. Chemistry Reviewer (Office of New Drug Quality Assessment)
Philip Colangelo, Ph.D. Clinical Pharmacology Team Leader (OCP/DCP4)
Dakshina Chilukuri, Ph.D. Clinical Pharmacology Reviewer (OCP/DCP4)
Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader (DSPTP)
Diana Willard, Chief, Project Management Staff (DSPTP)
Kristen Miller, Pharm.D., Regulatory Project Manager (DSPTP)

**MEETING OBJECTIVES:**

The purpose of the PSC is to:

- Ensure the Office of Drug Safety's (ODS) Division of Drug Risk Evaluation (DDRE) is aware of potential postmarketing safety problems with anidulafungin.
- Consider the need for any special postmarketing analyses/safety studies or evaluations to be agreed to by Pfizer prior to approval.
- Determine if there is any specific information or feedback that the Division would like from ODS.

**BACKGROUND:**

Pfizer's applications NDA 21-632 and 21-948 (anidulafungin) will be approved on or before February 17, 2006. Approvable actions were issued for NDA 21-632 on May 21, 2004 and November 25, 2005. A complete response to the November 25, 2005 approvable letter was received on January 24, 2006. The approval of anidulafungin will provide another echinocandin

treatment option for patients with the following serious infections: esophageal candidiasis, candidiasis and other *Candida* infections.

**DISCUSSION POINTS:**

Following introductions, an update on the status of the applications was provided. The following sections of the labeling were then discussed with regards to safety:

**PRECAUTIONS**

*Hepatic Effects*

DSPTP pointed out the existing paragraph on Hepatic Effects in the PRECAUTIONS section, noted that in clinical studies the event was judged to warrant a precaution comparable to statements in the approved caspofungin and micafungin labeling, and requested that DDRE particularly evaluate any post-marketing hepatic adverse event reports.

DDRE noted that liver function test (LFT) elevations are seen in many patients and expressed concern that more severe hepatic effects will be seen when anidulafungin is used in a larger population.

The Division noted that the population receiving anidulafungin is very sick and may have elevated LFTs prior to administration of anidulafungin. Additionally, the dose of anidulafungin used in the invasive candidiasis study is twice that used in the esophageal candidiasis study, and the LFT increase was not exaggerated. Finally, LFT elevations appear to be a class effect as they are seen in micafungin and caspofungin as well. The Division believes that the current labeling which recommends monitoring LFTs and hepatic function reflects the available clinical data, and post-marketing reports will be important for any updates.

DDRE recommended removing the phrase "has not been established" from the sentence "Isolated cases of significant hepatic dysfunction, hepatitis or worsening hepatic failure have been reported in these patients; a causal relationship to Eraxis has not been established." DDRE believes that the phrase is counterproductive as it does not encourage adverse hepatic events reporting. As a counterproposal, DDRE recommends the phrase "cannot be ruled out." The Division noted that "has not been established" is the wording in the labels for other echinocandin drugs, so it may be difficult to persuade Pfizer to accept the new proposed wording. DDRE recommended modifying all class labels.

**ADVERSE REACTIONS**

*Clinical Adverse Experiences*

DDRE noted that hyperkalemia was discussed in the medical officer's review, but that the information is not included in the labeling and asked about the severity of hyperkalemia. The Division stated that the severity was mild and that it occurred in both arms (drug-related hyperkalemia was less than 3% in each arm); therefore, the Division believes that with the data currently available there is no need to mention this is the label.

DDRE commented on the low numbers in the table entitled "Drug-related Adverse Events in Patients w/ Esophageal Candidiasis." The Division acknowledged that these are drug-related, not treatment emergent, adverse events. DDRE stressed consistency across labels so as not to unintentionally have one drug appear to cause less adverse events than the alternatives. It was noted that in fact the other two echinocandins, caspofungin and micafungin, have labeling that presents tables on drug-related adverse events.

Anidulafungin does not involve the cytochrome p450 metabolic enzymes, and in clinical studies there weren't other specific signals of concern identified, nevertheless DSPTP would like DDRE to monitor AERS for any signals or events that would need to be included in labeling.

Minutes recorder: Kristen Miller, Pharm.D.
Chair concurrence: Renata Albrecht, M.D.

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/s/

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Renata Albrecht
2/16/2006 09:48:51 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 14 2003

REGULATORY AFFAIRS

APR 18 2003

RECEIVED

Harriette Nadler, Ph.D.
Director, Regulatory Affairs
Versicor, Inc.
455.South Gulph Road, Suite 310
King of Prussia, PA 19406

**RE: Versicor, Inc., Small Business Waiver Request 2003.044 for Anidulafungin, NDA 21-632**

Dear Dr. Nadler:

This responds to your February 19, 2003, letter requesting a waiver of the human drug application fee for new drug application (NDA) 21-632 for anidulafungin under the small business waiver provision, section 736(d)(1)(D)[1,2] of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2003.044). For the reasons described below, the Food and Drug Administration (FDA) grants Versicor, Inc.'s (Versicor's) request for a small business waiver of the application fee for NDA 21-632 for anidulafungin.

According to your waiver request, Versicor is a small business with fewer than 500 employees, including employees of your affiliate, Biosearch Italia (Biosearch). You note that NDA 21-632 is indicated for treatment of esophageal candidiasis and is your first application submitted to FDA for review under section 505(b) of the Act. You also note that you do not have any affiliates who have previously filed NDAs. You anticipate submission of the NDA in April 2003.

Under section 736(d)(3)(B) of the Act[3] a waiver of the application fee is granted to a small business for the first human drug application that a small business or its affiliate[4] submits to the FDA for review. The small business waiver provision entitles a small business to a waiver when the business meets the following criteria: (1) the business must employ fewer than 500 persons, including employees of its affiliates, and (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

FDA's decision to grant Versicor's request for a small business waiver for NDA 21-632 for anidulafungin is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its letter dated March 25, 2003, that Versicor has fewer than 500 employees, including employees of its affiliate, Biosearch. Second, according to FDA records,

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[1] 21 U.S.C. 379h(d)(1)(D).

[2] On June 12, 2002, the President signed the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, which renumbered the small business waiver provision from section 736(d)(1)(E) to section 736(d)(1)(D) of the Act.

[3] 21 U.S.C. 379h(d)(3)(B).

[4] "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

the marketing application for anidulafungin, NDA 21-632, is the first human drug application, within the meaning of the Act, to be submitted to FDA by Versicor or its affiliates.

Consequently, your request for a small business waiver of the application fee for NDA 21-632 is granted, provided that FDA receives the marketing application for anidulafungin no later than March 25, 2004, 1 year after the effective date of the size determination made by SBA. Please include a copy of this letter with your application.

If FDA refuses to file the application or Versicor withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, Versicor should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether it continues to qualify for a waiver.

We have notified the FDA Office of Financial Management (OFM) of this waiver decision and have asked them to waive the application fee for NDA 21-632. According to our records, FDA was notified of payment of the application fee, $533,400, by Versicor for NDA 21-632 (user fee ID 4514) on April 1, 2003. You should receive a refund of $533,400. If you do not receive this refund within 30 days of the date of this letter, please contact Donna Simms, OFM, at 301-827-5042.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman, Michael Jones, or Tawni Schwemer at 301-594-2041.

Sincerely,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

IND 54,597
July 29, 2002 Pre-NDA Meeting

# MEMORANDUM OF MEETING MINUTES

| | |
|---|---|
| **MEETING DATE:** | July 29, 2002 |
| **TIME:** | 2:00 PM |
| **LOCATION:** | U.S. Food and Drug Administration<br>Center for Drug Evaluation and Research<br>Division of Special Pathogen and Immunologic Drug Products<br>9201 Corporate Blvd., S400<br>Rockville, MD 20850 |
| **APPLICATION:** | IND 54,597 (Anidulafungin Intravenous) |
| **TYPE OF MEETING:** | Pre- NDA Meeting |
| **MEETING CHAIR:** | Mark Goldberger, MD, MPH: Office Director (ODE IV) |
| **MEETING RECORDER:** | Kristen Miller, PharmD: Regulatory Project Manager |

## FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

| | |
|---|---|
| Mark Goldberger, MD, MPH | Office Director (ODE IV) |
| Renata Albrecht, M.D. | Acting Division Director (DSPIDP) |
| David L Roeder, M.S. | Assistant Director for Regulatory Affairs (ODE IV) |
| Marc Cavaille Coll, MD, Ph.D | Medical Officer Team Leader (DSPIDP) |
| Ekopimo O Ibia, MD, MPH | Medical Officer (DSPIDP) |
| Arturo Hernandez, M.D. | Medical Officer (Senior Staff Fellow- DSPIDP) |
| Cheryl A Dixon, Ph.D. | Statistician (DSPIDP) |
| Karen M Higgins, Sc.D. | Statistician Team Leader (DSPIDP) |
| Barbara M Davit, Ph.D | Clinical Pharmacology/Biopharmaceutics Team Leader |
| Kofi A Kumi, Ph.D. | Clinical Pharmacology/Biopharmaceutics (DSPIDP) |
| Owen G McMaster, Ph.D. | Pharmacologist (DSPIDP) |
| Peter A Dionne, M.S. | Microbiologist (DSPIDP) |
| Ellen C Frank, R.Ph | Chief, Project Management Staff (DSPIDP) |
| Kristen E Miller, PharmD | Regulatory Project Manager (DSPIDP) |

## VERSICOR ATTENDEES AND TITLES:

| | |
|---|---|
| Tim Henkel, MD, Ph.D. | Exec VP, Chief Medical Officer |
| David Krause, MD. | VP, Clinical and Medical Affairs |
| Tom Donnelly, Ph.D. | VP, Regulatory Affairs |
| Monica Lewis, Ph.D. | VP, Project Management |
| Martin Stogniew, Ph.D. | VP, PreClinical Development |
| Beth Goldstein, Ph.D. | Director, Clinical Microbiology |
| Harriette Nadler, Ph.D. | Director, Regulatory Affairs |
| Drew Sansone | Associate Director Regulatory Operations |
| Jim Dowell, Ph.D. | Associate Director, Pharmacokinetics |
| Judith Hoglind, Ph.D. | Director, Regulatory Affairs |

[ ] Consultant, Pharmacokinetics
[ ] Consultant, Electronic NDA
[ ] Consultant, Project Management

**BACKGROUND:** Versicor requested, and was granted, a meeting to discuss their new drug application for VER002 (anidulafungin), which has a goal submittal date of December 2002.

**MEETING OBJECTIVES:** Versicor sought concurrence from the Agency on a the format and content of the proposed NDA for anidulafungin for the treatment of esophageal candidiasis.

- Plans for an electronic-NDA/CTD hybrid submission
- Methods to analyze data for possible drug interactions
- Determination of MICs and breakpoints
- Resistance issues
- Individual study results to evaluate efficacy
- Clinical data grouping
- SAE narratives
- Datasets- format and content
- Provision of CRFs, CRTs, and Patient Profiles

**DISCUSSION POINTS:**

Recap of Questions the FDA Agreed with the Sponsor

After introductions, Versicor summarized all questions that the FDA agreed to during the internal meeting. These will be elaborated on during the discussion.
These included:

- The content of ISE (table of contents; no grouping of studies)
- The content of ISS (table of contents; study groups)
- The provision of SAEs occurring in Versicor-sponsored studies and Lilly phase 2/3 intravenous studies
- No patient profiles will be submitted
- The provision of electronic datasets from each of the completed Versicor-sponsored phase 1 and specific phase 2 or 3 studies
- The format of the datasets
- CRFs will be provided for deaths and discontinuations due to adverse events from all phase 1 and 2/3 intravenous studies

Overall NDA Format

Versicor proposed that the NDA will be fully electronic and be a hybrid of the traditional NDA format and the newer CTD format. It will be prepared in accordance with the 1999 FDA guidances,

"Providing Regulatory Submissions in Electronic Format- General Considerations", and "Providing Regulatory Submissions in Electronic Format- NDAs", with two exceptions. Items 4 and 5 will contain the headings/subheadings and order of presentation of the topics in accordance with the 2001 ICH guidances "M4Q: The CTD- Quality" and "M4S: the CTD - Safety", and will be provided in accordance with the 2001 FDA draft guidance "Submitting Marketing Applications According to the ICH-CTD Format- General Consideration". Proposed tables of contents for the sections to be presented according to the newer CTD format are enclosed in the briefing document. *The proposal is acceptable as proposed. It was clarified that it will be a hybrid of electronic NDA and CTD and not electronic CTD, guidance for which is yet to be finalized.*

Pharmacokinetics and Bioavailability

Versicor proposed to screen for covariate relationships with concomitant medications in a population pharmacokinetic analysis to address the possibility of drug interactions with anidulafungin. The analysis would pool anidulafungin pharmacokinetic data from ongoing phase 2 and phase 3 studies. *The Biopharm reviewers accepted this proposal, but clarified that this would only be acceptable as an initial screen. Depending upon the results, additional studies may by required to quantify the extent of any changes in PK parameters. It was also mentioned that the sponsor should consider study of CYP 450 inducers, particularly rifampin.*

Versicor acknowledged the comments and stated that they now know a lot more about the biotransformation of anidulafungin. In vitro studies show no CYP induction or liver involvement, adding that results were due to chemical degradation, so interaction with CYP 450 is very unlikely.

Clinical Microbiology

Because interpretive breakpoints currently cannot be established, Versicor proposed to continue collecting clinical data in order to correlate the efficacy of intravenous anidulafungin in treating candidiasis with *in vitro* sensitivity of the clinical isolates. Additionally, Versicor will continue to evaluate all factors that may influence inter-laboratory variability in MIC determinations. *The FDA agreed with this, but added that clinical microbiology data with patient ID, visit number, baseline pathogen, MIC, treatment regimen, clinical and mycological response with the day such measurements were made, etc should also be submitted.*

*The Agency acknowledged references cited in the briefing package on the cidality of anidulafungin. However, data to show convincingly that anidulafungin is fungicidal has not been reviewed. The sponsor agreed to submit data to document the cidality of anidulafungin in the NDA.*

Versicor proposed monitoring the emergence anidulafungin-resistant organisms during clinical studies, subsequently utilizing such organisms to investigate resistance mechanisms. *The Agency concurred.*

Clinical

**ISE:**

Versicor proposed providing individual study results, rather than integration of results across multiple studies to evaluate the efficacy of intravenous anidulafungin for the treatment of esophageal candidiasis. *The agency concurred with this, but questioned the value of preliminary data from Study 002-7.*

Versicor acknowledged that such data as in Study 002-7 does not provide much efficacy information, but that it can contribute to safety data because of the higher dose. [redacted] stressed that [redacted] sponsor [redacted] *The Agency reminded the sponsor of the concerns raised regarding the design of Study 002-7.*

**ISS:**

Versicor proposed grouping clinical data into (1) phase 1, (2) phase 2/3 and (3) oral formulation studies. *The Agency agreed.*

Versicor proposed submitting EKG data (>400) from studies 002-4, 002-5, 002-6, and 002-7 to provide information to assess the electrophysiologic effects, if any, of anidulafungin. The Agency asked for confirmation on the specifics, and Versicor verified that all 400 patients would be on anidulafungin. They continued, explaining that the study would comprise of a 12 lead done at baseline then repeated at some point in the future (close to Cmax at steady state). *The Agency concurred with this proposal, but added that this would remain a review issue pending the results of the preclinical electrophysiology study.*

The sponsor provided a proposed table of contents and a description of all clinical pharmacology studies to be included in the NDA. *The Agency accepted these proposals and is satisfied with the studies to be included in the NDA.*

Other Issues

**SAEs:**

Versicor stated that they would provide narratives for all SAEs occurring in Versicor-sponsored studies and Lilly Phase 2/3 intravenous studies. *The Agency stated that narratives should be included for all SAEs from all studies.*

Versicor reported that there were no SAEs in the phase 1 studies and that there is only a small number of SAEs in efficacy studies from Lilly (less than 10). They also agreed to include SAEs

from the oral studies in the NDA. *The Agency informed the sponsor that any documentation would be helpful because of the leanness of the data.*

**Patient Profiles:**

Versicor stated that they are not planning to provide patient profiles. *The Agency concurred.*

Case Report Tabulations

Regarding datasets to be provided, Versicor proposed providing electronic datasets from each of the complete Versicor-sponsored phase 1 and specific phase 2 or 3 studies (Studies 002-4, 002-6, and XBAF). They continued, stating that selected patient datasets relative to early phase 1 studies conducted by Lilly are unavailable (101L, XBAE, and XBAU), and that datasets with limited numbers of patients, e.g., XBAG and Study 002-11, would not be provided. *The Agency requested some clarification, and* Versicor said that Study 002-11 was ongoing, but datasets would be provided when the study is completed and that XBAG only had 3 patients. The sponsor then reiterated that there were no deaths in the phase 1 studies, and no deaths or discontinuations in Study 101L. *The Agency maintained that all datasets should be provided, especially given the leanness of the database. The sponsor consented and agreed to provide data listings for Lilly's Study 101L.*

Versicor proposed content of the data definition tables. *The Agency agreed, provided that the sponsor sends the analysis datasets, and that derived variables and captured data are supplied.*

Case Report Forms

Versicor proposed to provide CRFs for deaths and discontinuations due to Adverse Events from all phase 1 and 2/3 intravenous studies. *The Agency agreed.*

Other Discussion Points

*The Agency asked if the goal submission date was still the fourth quarter of 2002.* The sponsor confirmed the goal date, but admitted that it may be pushed back into the first quarter of 2003.

*The Agency reiterated the overall leanness of the database, bringing attention to the non-inferiority design, the use of the lowest approved dose of comparator, and the fact that the indication is relatively less serious. Due to all of these issues, there is limited room for unanticipated problems*

*The Agency requested a few clarifications regarding the clinical studies.* Versicor verified that on page 96 of the Briefing Package, the N for each dose cohort for Study 002-6 should read 40, not 60. In addition, the sponsor confirmed that all 120 patients in Study 002-6 will be included, resulting in 481 patients exposed to 14 days or more, and of these, 442 patients received 50 mg or more. Versicor added that these numbers were only approximations though.

*The Agency acknowledged that Versicor has planned pediatric phase 1 pharmacokinetic studies in children two to twelve years of age, but questioned what the sponsor's intentions were regarding children younger than two years old, and age 12 to 16 years old.* Versicor responded that the planned study is a single dose, dose-ranging study, and that they felt it was a practical first step. They further noted the difficulties in doing pediatric studies for the indication of esophageal candidiasis and stated that they will be asking for a waiver from pediatric studies.

*The Agency questioned the intention of the inclusion to the NDA of the six patients from Study 002-11. The Agency also wanted to confirm that the definition of fluconazole resistant was oropharyngeal candidiasis (OPC) and/or esophageal candidiasis (EC) that failed 14 days of treatment with at least 200 mg daily of fluconazole.* The sponsor confirmed this definition and added that the cases were not based on *in vitro* resistance testing. Versicor stated that the purpose of the inclusion of the preliminary data from Study 002-11 would be to contribute to the safety and efficacy database, and to the population pharmacokinetic study for potential drug interactions since the patients are from the United States only and are on antiretroviral therapy. On further questioning, Versicor stated that the inclusion was for completeness sake, not because they are seeking any indication or specific labeling. However, the sponsor went on to state that some fluconazole resistant strains may be isolated in Study 002-6 as well, and depending on the number, they may seek additional advice from the Agency. *The Agency agreed to review such data.*

**ACTION ITEMS**

1. The Agency is requesting that Versicor share sham datasets.

**Minutes Preparer: Kristen Miller, Project Manager**

**Chair Concurrence: Mark Goldberger, MD, MPH: Office Director (ODE IV)**

Drafted by: KEM/8/2/02

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

/s/

Mark Goldberger
10/11/02 10:16:51 AM

# APPENDIX A: FDA CLINICAL DEVELOPMENT MEETING MINUTES

**VER002 (anidulafungin), IND 54,597**

Meeting date: January 31, 2002
Time: 11AM

**FDA Division of Special Pathogens and Immunologic Drug Products Attendees:**

| Name: | Title: |
|---|---|
| Mark Goldberger, M.D.,M.PH. | Acting Office Director ODE IV |
| Renata Albrecht, M.D. | Acting Division Director; Division of Special Pathogen and Immunologic Drug Products |
| Ekopimo O. Ibian, M.D. | Medical Officer Reviewer |
| Marc W. Cavaille Coll M.D., Ph.D. | Medical Officer Team Leader |
| Kofi A. Kumi, Ph.D. | Clinical Pharmacology Reviewer |
| Funmilayo O. Ajayi, Ph.D. | Clinical Pharmacology Team Leader |
| Cheryl A. Dixon, Ph.D. | Statistician Reviewer |
| Karen M. Higgins, Ph.D. | Statistician Team Leader |
| Linda L. Gosey | Microbiology Reviewer |
| Shukal Bala, Ph.D. | Microbiology Team Leader |
| Owen G. McMaster, Ph.D. | Pharmacology Reviewer |
| Kenneth L. Hastings, Ph.D. | Pharmacology Team Leader |
| Ellen C. Frank, R.Ph. | Chief Project Management Staff |
| Sary Beidas, M.D. | Medical Officer |
| Leo Chan, R.Ph. | Regulatory Project Manager |

**Attendees from Versicor, Inc.:**

| Name: | Title: |
|---|---|
| Timothy Henkel, M.D., Ph.D. | Chief Medical Officer |
| Thomas Donnelly, Ph.D. | Vice President, Regulatory Affairs and Compliance |
| Monica Lewis, Ph.D. | Vice President, Project and Alliance Management |
| Martin Stogniew, Ph.D. | Vice President, Preclinical Development |
| Beth Goldstein, Ph.D. | Director, Clinical Microbiology |
| Harriette Nadler, Ph.D. | Director, Regulatory Affairs |
| [redacted] | Medical Consultant |
| [redacted] | Medical Consultant |
| [redacted] | Pharmacokinetics Consultant |
| Georgina Kilfoil | Project Manager |

**Summary:** The objective of this face-to-face meeting was to discuss the proposed NDA for treatment of esophageal candidiasis and the clinical and nonclinical development plans for anidulafungin.

**Specific topics included:**
Versicor's introductory comments and previous FDA advisories
Pharmacokinetic data
Interaction with cyclosporine A
Nonclinical data
Potential interaction with glucocorticoids
Proposed NDA for treatment of esophageal candidiasis
Phase II/III study in invasive aspergillosis
Phase III study in patients with invasive candidiasis and candidemia

**Discussion topic 1**: Versicor's introductory comments and previous FDA advisories

Versicor presented an overview of the questions posed to the Division in the July 19, 2001 briefing package and the proposed NDA for treatment of esophageal candidiasis. The Division apologized for the 6 mos. delay in scheduling a face-to-face meeting with Versicor, Inc. due to other conflicting priorities for the Division.

Dr. Goldberger asked if Versicor was [ ] treatment of [ ] esophageal candidiasis [ ] He further noted that if this is planned, data in that patient subset are needed to support the indication. Versicor responded that the data [ ]

Dr. Goldberger asked about Versicor's expectation vis a vis fluconazole. Versicor described the design of the pivotal study (noninferiority, 90% power, 10% delta with respect to the lower limit of the confidence interval) using the 100 mg loading dose followed by the 50 mg daily maintenance dose for anidulafungin; 200 mg loading dose followed by a 100 mg maintenance dose for fluconazole). The Division requested that Versicor, Inc. discuss the clinical program for VER002 in terms of the magnitude and duration of dosing. Versicor presented an overview using the slides that were submitted to IND 54,597 on January 9, 2002; Serial No. 077.

The Division reviewed issues from the Jan. 21, 2001 teleconference. They noted that the proposed NDA is for a less severe indication than that for caspofungin (invasive aspergillosis), thus the number of patients may be low. The Division asked if the total number of patients treated in VER002-4, 6, and 7 at the proposed dose (or higher) for labeling was 370. Versicor replied yes.

The Division stated that the dose and duration of fluconazole used in the phase III study were at the lower end of the approved dosing regimen and did not allow the increase in the fluconazole dose stated in the label. Another issue they noted was the use of a single

pivotal study with a single-sided alpha of 0.05. They also mentioned that the sample size and exposure are sufficient for this indication but that the VER002-4 study has issues that may need to be addressed by the FDA Advisory Committee, e.g., the 100 mg dose of fluconazole with a non-inferiority design. They further mentioned that VER002-4 is well-designed but that it may be difficult to show clinical benefit with the 100 mg of fluconazole together with a shorter duration of dosing. They also noted that the 100 mg dose of fluconazole is used for diseases that are less serious than esophageal candidiasis. Versicor responded that the fluconazole dose is in accordance with the IDSA guidelines and is an approved labeled dosage for fluconazole in the treatment of esophageal candidiasis. The Division acknowledged that it was consistent with IDSA guidelines and approved dosing.

Dr. Albrecht replied that the program is well-designed but lean and will be satisfactory--if the goals are met. She also stated that if an unexpected safety finding is observed in such a small database, there is no latitude. She mentioned that regulatory decisions will be challenging and unanticipated safety findings may be reflected in the labeling. Versicor responded that many endpoints were to be employed, e.g., relapse rates, and that anidulafungin has fungicidal activity, which may represent a medical advance relative to fluconazole. The Division stated that a strong finding is needed for the primary endpoint before secondary endpoints are considered. They asked whether anidulafungin was cidal. Versicor replied yes and that animal models showed sterilization of organs. The Division asked if they could be provided with data demonstrating fungicidal activity.

The Division stated that for a one-sided statistical test, they want an alpha of 0.025, not [redacted] as proposed by Versicor. Versicor replied that the ICH guidance recommended an alpha of 0.025 only in the instance of a drug with safety concerns. Dr. Goldberger emphasized that use of 0.025 was the policy throughout the Center. The Division also acknowledged that this would require ~50 additional patients per arm. Versicor replied that this issue would be re-evaluated.

Dr. Goldberger stated that the use of one substantial phase III study supported by small phase II dose-ranging studies mandates that the phase III study be well-sized and that the Division and Versicor must agree on the statistical approach. Dr. Albrecht discussed the FDA regulation requesting adequate well-controlled investigations which is typically fulfilled by conducting two studies for the indication. They recognize the need to be flexible since this is not the usual anti-infective indication. They further noted that this is a focused indication. Hence they will consider one pivotal study corroborated by supportive data from phase II, but statistical design is important. They also stated that the phase III study results must be robust.

Dr. Goldberger asked if Versicor was comfortable with the dose used for phase III in esophageal candidiasis. Versicor replied yes, that the organisms are almost all *Candida albicans* with exceedingly low MICs and that in the phase II study for this indication, the phase II data suggest a dose response. They further noted that the spectrum of organisms is different for invasive candidiasis, therefore, it is important to conduct dose-ranging

studies. Dr. Goldberger replied that if the esophageal candidiasis indication ultimately became approved, the labeling would state the dose of fluconazole used.

**Discussion topic 2: Pharmacokinetic data**

The Division mentioned that the briefing document stated that anidulafungin was not a substrate for CYP450 enzymes. They asked for the data. Versicor responded that raw data was available to support this statement. The Division replied that it is not clear whether the drug is an inducer or inhibitor of CYP450. Versicor agreed to provide data from several *in vitro* studies which addressed this question. (Post-meeting note: The data was provided in the Investigator's Brochure, pg 20-22, Tables 4-5 and 4-6, submitted to IND 54,597 on November 30, 2001; Serial No. 071).

The Division stated that a minimum of six evaluable patients is preferred for mass balance studies. Versicor agreed to submit the mass balance protocol.

**Discussion topic 3: Interaction with cyclosporine A**

The Division asked whether the cyclosporine interaction study was completed. Versicor replied that the sponsor now has data to show tolerability and pharmacokinetics of the coadministered drugs. The Division further inquired about the rationale behind omitting studies on the effect of anidulafungin on cyclosporine, i.e., only the converse effect was studied. Versicor stated an *in vitro* study had shown that there was no effect of anidulafungin on cyclosporine metabolism. Consequently, a clinical study was not done. Furthermore, the data available for caspofungin indicate the effect of interest is that of cyclosporine on the echinocandin.

The Division asked about other planned drug interaction studies, e.g., tacrolimus, anti-retroviral agents, and rifampin. Versicor replied that tacrolimus was not relevant to the target population for the 1st NDA, [redacted] The Division discussed the surprise findings that occurred with caspofungin during the clinical program, i.e., the *in vitro* CYP450 studies did not fully predict metabolic interaction with drugs, e.g., nelfinavir. They further noted that other distribution-based mechanisms could have been involved.

Versicor responded that population pharmacokinetics was being monitored during all studies, including the fluconazole-refractory study in mucosal candidiasis. In this latter study, patients will also be receiving triple anti-retroviral therapy. The Division stated that labeling will reflect the interactions observed and hence it is prudent to raise the issues at the start, e.g., at the time of phase II dose-ranging studies. They also mentioned that population pharmacokinetics was not helpful with caspofungin. They further stated that Versicor needs to look for concentration effects and do a covariate analysis. Versicor responded that they intended to do that and also explore PD:PK relationships for each of the three dosing regimens.

**Discussion topic 4: Nonclinical data**

The Division stated that there is adequate toxicology coverage for 14-21 days of human dosing. Six-month toxicology studies are needed for long-term treatment in other indications, [ ] They noted that treatment in the ongoing invasive aspergillosis study could be up to 90 days. They also inquired about the phototoxicity and segment III studies. Versicor replied that the phototoxicity study report would be submitted to the Division soon and that the segment III studies would be completed by August, 2002. They also noted that the 6-month study in rats was planned. The Division asked about the QT effect study. Versicor responded that the study was complete and the report would be submitted to the Division.

The Division stated that they were concerned about potential immunotoxicity, which may be signaled by the thymic necrosis seen in the 3-month rat study. They mentioned that the findings could represent a toxicity stress phenomenon or a drug-induced immuno-modulating phenomenon. [

] They offered to review proposed protocols and provide comments. They stated that there is not a huge safety margin, i.e., factor of ~3, rather than 10-20. Versicor replied that the margin is ~6 for the proposed NDA, i.e., esophageal candidiasis. Versicor replied that the FDA input would be considered.

**Discussion topic 5: Potential interaction with glucocorticoids**

The Division agreed with Versicor that the Stevens et al study was flawed in terms of strain selection, number of mice, choice of doses for both anidulafungin and the glucocorticoid, diluent, statistics, and reproducibility. They also noted that it is not clear that toxicity would be found with coadministration in man. However they recommended that Versicor design a study to address this question. This is their conservative position as it is still possible that there may be an interaction under more relevant conditions.

The Division offered to help design a protocol for a better study, which would provide a more definitive answer regarding a possible interaction. Versicor replied that they had an appropriate rabbit study with more relevant doses in a species with similar pharmacokinetics to that of man. The Division responded that they will consider the other study but that Versicor needs to go back to the mouse strain (DBA/2) used by Stevens et al and design a new study with an optimized design. Versicor asked whether it was surprising to see toxicity at ~4X LD50. The Division replied that a bad study with bad results can't be ignored and a good study needs to be performed.

The Division stated that if another study is not performed, the labeling will reflect the Stevens et al data. They also mentioned that it is in the interest of Versicor to conduct another study and that the additional study should be reported with the NDA. Versicor replied that the Division's input would be considered.

**Discussion topic 6: Question: Proposed content of the NDA in esophageal candidiasis**

The Division restated that one large study with a non-inferiority design and a 100 mg dose of fluconazole provides little flexibility. They further mentioned that less than robust findings with the primary endpoint could not be saved by other endpoints and that the size of the database is on the lean side to exclude risk with a modest effect. They also stated that the FDA Advisory Committee will characterize the benefit: risk ratio, e.g., the preference for oral vs parenteral drugs for this type of indication, and the available oral therapeutic alternatives, given the relatively less severe indication. They also mentioned that Versicor is not targeting azole-refractory patients in phase III and only up to 6 refractory patients are expected to be included in the filing.

Dr. Goldberger asked whether there were other factors beyond resistance that could affect the response to antifungal therapy. Dr. Rex replied that there were patient characteristics making the refractory patients more difficult to treat, i.e., their immunocompromised status, especially when their disease has progressed. In addition, these patients have limited treatment options, e.g., amphotericin B with its well-known toxicity profile. The Division replied that the filing will be strengthened if more than the anticipated 6 refractory patients are included and that resistant strains need to be highlighted in the filing. Versicor responded that *Candida spp, other than C. albicans,* and strains from fluconazole-refractory cases will be highlighted in the filing.

The Division stated that the NDA as proposed is 'fileable' and may be approvable--depending on the results. There is no room for less than robust findings. Dr. Goldberger replied that the phase III study may help differentiate the effectiveness of oral vs parenteral therapy in this target population. Versicor responded that salivary and mucosal levels of anidulafungin in volunteers were not performed. The Division asked whether any interim analyses were to be conducted. Versicor responded no.

**Discussion topic 7: Question:** [

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**Question 8: Phase III study in patients with invasive candidiasis and candidemia**

Versicor asked the Division for input regarding the use of AmBisome® as a comparator for the phase III study in invasive candidiasis and candidemia. The Division replied that AmBisome® is not approved for the indication so equivalence to an unapproved drug, or a drug which the Division has not agreed is efficacious and safe in the indication, will not gain approval for anidulafungin in the indication. A literature review was presented in the briefing document including some studies with strong evidence that liposomal amphotericin may be more effective than amphotericin B deoxycholate. But the Division needs to receive the data behind the summaries. Much of the literature reviewed involved safety studies, small studies, or studies for the treatment of febrile neutropenic patients with few organisms recovered. Hence such studies are not sufficiently robust to help decision-making. There are also confounding factors causing fever in the febrile neutropenia studies. Versicor agreed to provide the literature cited. They also mentioned that the phase III study would not start for one year. Versicor wants to work with the Division on the design of this study and plans to conduct a randomized controlled study.

Dr. Albrecht noted that the clear path to gain regulatory approval is to show superiority of anidulafungin over the comparator but it is not easy to do using an effective product as comparator. They suggested providing publications showing support for the comparator as safe and effective and to provide raw data if available. Data from unpublished investigations should be included if possible. The Division and the FDA Advisory Committee need convincing data to make regulatory decisions. Versicor asked whether the Division would consider results if the drug were equivalent in efficacy using a non-inferiority design but superior in terms of safety and tolerability. Dr. Albrecht replied that any convincing differences that are clinically relevant are of interest. The Division added that re: superiority in terms of safety and tolerability, Versicor needs to show that AmBisome® has the expected effect versus placebo. The confidence limit with the product must exclude the range seen with placebo.

*Overall:*

The meeting ended with staff from Versicor and the Division having brief off-line discussions which were complimentary in terms of the briefing document and our other preparations for the meeting, the positive interactions during the meeting, and the agreements reached. Both groups look forward to future meetings and continued collaboration on the development of anidulafungin to best meet patient needs in a timely manner.

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