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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-632

NDA 21-948

Approvable Letter (S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-632

Vicuron Pharmaceuticals, Inc.
c/o Pfizer, Inc.
Attention: Maureen H. Garvey, Ph.D.
Senior Director, Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
235 East 42nd Street 605/5
New York, NY 10017

Dear Dr. Garvey:

Please refer to your new drug application (NDA) dated and received on April 25, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for $\text{C}_{17}\text{H}_{15}\text{FO}_4$ (anidulafungin) for Injection, 50mg.

We acknowledge receipt of your submissions dated:

May 27, 2005
November 1, 2005
November 23, 2004

September 16, 2005
November 10, 2005

October 25, 2005
November 15, 2005

The May 27, 2005, submission constituted a complete response to our May 21, 2004, action letter.

We completed our review of this application for the treatment of patients with esophageal candidiasis, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. Provide revised Final Printed Labeling (FPL) responsive to the attached Package Insert draft.

2. Revise the carton and container labels as described below:

A. CONTAINER LABEL (Anidulafungin 50 mg)

1. Include the route of administration on the principal display panel.
2. Include the resultant concentration following reconstitution of the product. For example: Once reconstituted with 15 mL of ..., each mL contains ...mg anidulafungin.
3. If space permits, add a statement to discard the unused portion.
4. If space permits, add a statement to dilute to 0.5 mg/mL in an appropriate infusion solution prior to administration.

B. CONTAINER LABEL (Diluent Vial)

1. Revise the label so that only the established name and strength of the diluent appear in prominent print on the principal display panel to reduce confusion that this vial contains the active drug. Delete "Diluent for ...50 mg".
2. If space permits, add a statement to discard the unused portion.
3. Include the volume of the vial contents.
4. Include the route of administration on the principal display panel.
5. Revise the statement on the side panel, "Reconstitute...Injection.", to read, "Each mL contains...", and "This product is supplied for dilution of [redacted] Use 15 mL of..."

C. CARTON LABELING (1 unit and 10 units)

1. Include the expected concentration of [redacted] after reconstitution.
2. Since this product includes two components, drug vial and diluent vial, revise carton labeling on each panel to indicate that both components are within the carton. For example, "Each carton contains: 1 vial of 50 mg anidulafungin, 1 vial of ... (diluent)".
3. Increase the prominence of the route of administration on the principal display panel.
4. Relocate the statement, "Single-use vials" to appear at the top the principal display panel, rather than below the established name and strength.
5. Add a statement to dilute to 0.5 mg/mL in an appropriate infusion solution prior to administration.

We also note that the data submitted were insufficient to support inclusion of information for [redacted] in the product label. Additional data in [redacted] are needed to allow a conclusive evaluation of anidulafungin in this clinical situation.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a re-tabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with the Division of Special Pathogen and Transplant Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Judit Milstein, Chief Project Management Staff at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

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

**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
11/25/2005 03:23:30 PM
for Mark J. Goldberger, MD MPH



NDA 21-632

Vicuron Pharmaceuticals Inc.
Attention: Harriette Nadler, Ph.D.
Director, Regulatory Affairs
355 South Gulph Road, Suite 310
King of Prussia, PA 19406

Dear Dr. Nadler:

Please refer to your new drug application (NDA) dated April 25, 2003, received April 25, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [] (anidulafungin) for Injection.

We acknowledge receipt of your submissions dated:

June 23, 2003	January 6, 2004	March 5, 2004
July 16, 2003	January 14, 2004	March 9, 2004 (2)
August 22, 2003	January 23, 2004	March 10, 2004
September 5, 2003	January 30, 2004	March 16, 2004
October 14, 2003	February 13, 2004 (2)	April 13, 2004
October 22, 2003	February 24, 2004	April 27, 2004 (2)
November 25, 2003	March 3, 2004	
November 26, 2003	March 4, 2004	

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, it will be necessary for you to address the following deficiency:

- 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.

When you respond, it will be necessary for you to submit draft labeling revised to reflect additional safety or efficacy data submitted.

In addition, when you respond, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.

- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the above bullet.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Special Pathogen and Immunologic Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

{See appended electronic signature page}

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

**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
5/21/04 12:49:08 PM
for Mark J. Goldberger, MD MPH
