

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-632**

**NDA 21-948**

**Chemistry Review(s)**

**NDA 21-632**

**NDA 21-948**

**ERAXIS™  
(anidulafungin)  
For Injection**

**Pfizer Pharmaceuticals Inc.**

**Mark R. Seggel  
Office of New Drug Quality Assessment  
Division of Pre-Marketing Assessment II  
Branch IV**

# Table of Contents

**Table of Contents .....2**

**Chemistry Review Data Sheet.....4**

**The Executive Summary .....8**

**I. Recommendations..... 8**

A. Recommendation and Conclusion on Approvability ..... 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... 8

**II. Summary of Chemistry Assessments .....8**

A. Description of the Drug Product(s) and Drug Substance(s) ..... 8

B. Description of How the Drug Product is Intended to be Used..... 9

C. Basis for Approvability or Not-Approval Recommendation..... 9

**III. Administrative..... 10**

A. Reviewer’s Signature..... 10

B. Endorsement Block..... 10

C. CC Block ..... 10

**Chemistry Assessment ..... 11**

**I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data ..... 11**

**S DRUG SUBSTANCE..... 11**

**P DRUG PRODUCT ..... 11**

**A APPENDICES ..... 11**

A.1 Facilities and Equipment (biotech only) ..... 11

A.2 Adventitious Agents Safety Evaluation ..... 11

A.3 Novel Excipients ..... 12

**R REGIONAL INFORMATION..... 12**

R1 Executed Batch Records .....12

R2 Comparability Protocols .....12

R3 Methods Validation Package .....12

**II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1 ..... 13**

**A. Labeling & Package Insert..... 13**

**B. Environmental Assessment Or Claim Of Categorical Exclusion..... 16**

**III. LIST OF DEFICIENCIES TO BE COMMUNICATED..... 17**

*Appears This Way  
On Original*

# Chemistry Review Data Sheet

1. NDA 21-632 (Re-submission)  
NDA 21-948

2. REVIEW #: 2

See Chemistry Review #1 (NDA 21-632 Drug Substance) prepared by Dr. Balajee Shanmugam for drug substance CMC and Chemistry Review #1 (NDA 21-632 Drug Product) prepared by M. Seggel.

3. REVIEW DATE: 17-FEB-2006

4. REVIEWER: Mark R. Seggel, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
N21-632 Original NDA	25-APR-2003
BC (info for Methods Validation Package)	25-NOV-2003
BC (product quality microbiology update)	14-JAN-2004
BC (drug substance update)	30-JAN-2004
BC (stability update)	13-FEB-2004
BC (drug substance and drug product updates)	24-FEB-2004
BC (drug substance and drug product updates)	03-MAR-2004

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
N21-948 Original NDA	18-AUG-2005
N21-632 1 <sup>st</sup> Resubmission	27-MAY-2005
N21-632 2 <sup>nd</sup> Resubmission	24-JAN-2006
N21-948 (EA – claim for cat. exclusion)	16-FEB-2006
N21-632/N21-948 (labeling)	16-FEB-2006

## 7. NAME &amp; ADDRESS OF APPLICANT:

On September 14, 2005, Vicuron Pharmaceuticals, the original owner of these New Drug Applications, was acquired by Pfizer. At that time, Pfizer was authorized to act as agents on behalf of Vicuron.

Name: Pfizer Inc.  
Address: East 42<sup>nd</sup> Street 605/5  
New York, NY 10017  
Representative: Maureen H. Garvey, PhD  
Senior Director, Worldwide Regulatory Strategy  
Worldwide Regulatory Affairs and Quality Assurance  
Telephone: 212-733-5688

Name: Vicuron Pharmaceuticals Inc.  
Address: 455 South Gulph Road  
King of Prussia, PA 19406  
Representative: Harriette L. Nadler, PhD  
Senior Director, Regulatory Affairs  
Telephone: 610-491-2211

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ERAXIS<sup>TM</sup> (originally proposed  )<sup>(1)</sup>  
b) Non-Proprietary Name (USAN): anidulafungin  
c) Code Name/# (ONDC only): VER002; LY303366;  
d) Chem. Type/Submission Priority (ONDC only):  
• Chem. Type: N21-632 Type 1  
N21-948 Type 6  
• Submission Priority: N21-632 S  
N21-948 P

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

## 10. PHARMACOL. CATEGORY: Systemic antifungal

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: 50 mg/vial

13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):  
 SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

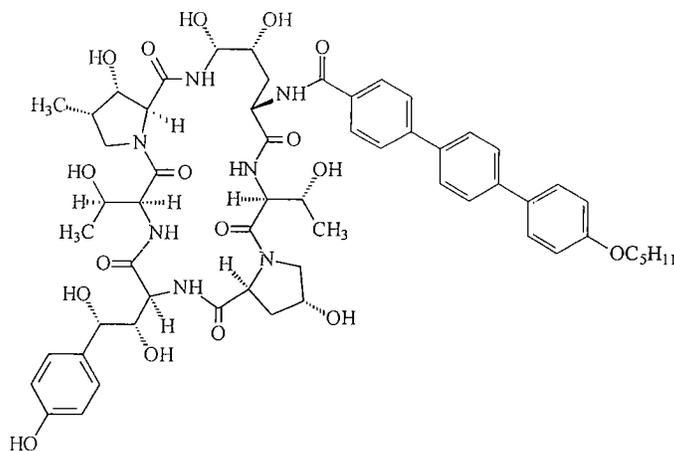
Echinocandin B, 1-[(4R,5R)-4,5-dihydroxy-*N*<sup>2</sup>-[[4''-(pentyloxy)[1,1':4',1''-terphenyl]-4-yl]carbonyl]-L-ornithine]-

(4R,5R)-4,5-Dihydroxy-*N*<sup>2</sup>-[[4''-(pentyloxy)-p-terphenyl-4-yl]carbonyl]-L-ornithyl-L-threonyl-*trans*-4-hydroxy-L-prolyl-(*S*)-4-hydroxy-(*p*-hydroxyphenyl)-L-threonyl-L-threonyl-(3*S*,4*S*)-3-hydroxy-4-methyl-L-proline cyclic (6→1)-peptide

Molecular formula: C<sub>58</sub>H<sub>73</sub>N<sub>7</sub>O<sub>17</sub>

Molecular weight: 1140.27

CAS: 166663-25-8



# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	III			3, 4	Adequate	12-FEB-2003	-
	III			3, 4	Adequate	06-AUG-2003	-

\*The [ ]

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type I DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

#### B. Other Documents:

See Chemistry Review #1, Drug Product CMC

### 18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		
EES	Acceptable	25-JUL-2003 26-AUG-2005	S. Ferguson, HFD-322
Pharm/Tox	n/a		
Biopharm	n/a		
LNC	n/a		
Methods Validation	n/a		
DMETS	Trademark acceptable; other labeling recommendations conveyed to applicant	02-DEC-2003 13-FEB-2006	C. Hoppes, HFD-420
EA	Categorical exclusion acceptable	16-MAY-2003 16-FEB-2006	M. Seggel
Microbiology	Acceptable	25-FEB-2004	J. McVey, HFD-805

# The Chemistry Review for NDA 21-632 and NDA 21-948

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The applications, as amended, are recommended for approval from the chemistry, manufacturing and controls perspective.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no recommendations for Phase 4 CMC commitments. The applicant will continue to monitor the stability of the drug substance and drug product. The applicant will also re-evaluate the drug substance and drug product specifications after the manufacture of ten commercial batches of each.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

See Chemistry Review #1, Drug Substance CMC for NDA 21-632 and Chemistry Review #1, Drug Product CMC for NDA 21-632.

The drug product is a lyophilized sterile solid containing 50 mg of the antifungal agent anidulafungin. The product is reconstituted and diluted prior to intravenous infusion. A 20% (w/w) ethanol diluent is provided for reconstituting the lyophilized product. The commercial package will contain two 15 mL vials. One vial contains 50 mg of anidulafungin and the second contains the diluent used for reconstituting the drug product. The manufacture of the drug product is straightforward. Common, compendial-grade excipients are used and include fructose, mannitol, tartaric acid, polysorbate 80, and sodium hydroxide and/or hydrochloric acid to adjust the pH. The formulation is [redacted] and lyophilized. The identity, strength, quality and purity of the drug product are assured by release testing appropriate for a product for intravenous administration. The drug product exhibits good stability at 25°C/60% RH. The diluent is simply a 20% aqueous ethanol solution that has been [redacted]

## Executive Summary Section

Anidulafungin is a semisynthetic antifungal lipopeptide (cyclic hexapeptide with lipophilic acyl side chain) derived from echinocandin B. It has activity against pathogenic fungi including *Candida* spp. The echinocandins, and structurally related pneumocandins, inhibit the enzyme  $\beta$ -1,3-D-glucan synthetase.  $\beta$ -(1,3)-D-Glucan, a polymer of glucose, is an integral component of the fungal cell wall. The drug substance is insoluble in water and slightly soluble in ethanol. It has good chemical stability, but the recommended storage condition is [ ] The identity, strength, quality and purity of the drug substance are assured by appropriate stability-indicating tests.

**B. Description of How the Drug Product is Intended to be Used**

Anidulafungin for injection is indicated for the treatment of esophageal candidiasis (NDA 21-632) and Candidemia and other forms of *Candida* infections (NDA 21-948). The intended dosing regimen for the treatment of esophageal candidiasis is a 100-mg loading dose followed by a 50-mg daily maintenance dose for the duration of treatment. For invasive candidiasis, a 200-mg loading dose will be followed by 100 mg daily dosing. The lyophilized drug product requires two dilutions prior to infusion: dilution with the 20% (w/w) dehydrated alcohol/water for injection diluent and subsequent dilution with either 5% Dextrose Injection USP (D5W) or 0.9% Sodium Chloride Injection USP. The final concentration of the infusion solution is 0.5 mg/mL.

The stability studies support an expiration dating period of 30 months for product stored at 25°C/60% RH. The reconstituted solution is stable for up to [ ] while the infusion solution is stable for up to [ ] s. However, the reconstituted solution should be used within 24 hours of preparation to insure microbiological quality.

**C. Basis for Approvability or Not-Approval Recommendation**

The physicochemical properties of the drug substance have been adequately characterized. The manufacturing process is adequately described. Suitable controls for the drug substance have been established. The stability of the drug substance has also been adequately characterized and appropriate storage conditions established.

The components and composition of the drug product have been adequately specified. The inactive ingredients are commonly used in this dosage form and are of suitable quality. The manufacturing process has been adequately described.

Additional details regarding the manufacture of the drug substance have been provided by the applicant as requested. All issues regarding the drug substance and drug product specifications have been adequately negotiated with the applicant. The applicant will continue to monitor the stability of the drug substance and drug product. The applicant



Executive Summary Section

will also re-evaluate the drug substance and drug product specifications after the manufacture of — commercial batches of each.

The manufacturing and testing facilities have acceptable cGMP status and the Office of Compliance has issued an Overall Recommendation of Acceptable for the NDA.

The relevant sections of the Package Insert and the container/carton labels have been revised as requested by the chemistry reviewer and DMETS. As revised, the labeling is acceptable.

**III. Administrative**

**A. Reviewer's Signature**

*{see Electronic Signature Page}*

**B. Endorsement Block**

ChemistName/Date: Same date as draft review  
ONDQA/DPAII BC/Div.Dir. Name/Date

*{see Electronic Signature Page}*

**C. CC Block**

*See dfs*

7 Page(s) Withheld



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

       § 552(b)(5) Deliberative Process

       § 552(b)(4) Draft Labeling

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

/s/

-----  
Mark Seggel  
2/17/2006 09:13:07 AM  
CHEMIST  
N21632/N21948

Elaine Morefield  
2/17/2006 10:14:04 AM  
CHEMIST



**NDA 21-632**

[ ]  
**(anidulafungin)**  
**For Injection**

**Vicuron Pharmaceuticals Inc.**

**Mark R. Seggel**  
**HFD-590**  
**Division of Special Pathogen and**  
**Immunologic Drug Products**



# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>5</b>
<b>The Executive Summary .....</b>	<b>9</b>
<b>I. Recommendations .....</b>	<b>9</b>
A. Recommendation and Conclusion on Approvability .....	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	9
<b>II. Summary of Chemistry Assessments.....</b>	<b>9</b>
A. Description of the Drug Product(s) and Drug Substance(s) .....	9
B. Description of How the Drug Product is Intended to be Used .....	10
C. Basis for Approvability or Not-Approval Recommendation.....	10
<b>III. Administrative.....</b>	<b>11</b>
A. Reviewer's Signature.....	11
B. Endorsement Block.....	11
C. CC Block .....	11
<b>Chemistry Assessment.....</b>	<b>12</b>
<b>I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....</b>	<b>12</b>
<b>S DRUG SUBSTANCE.....</b>	<b>12</b>
<b>P DRUG PRODUCT.....</b>	<b>13</b>
<b>P.1 Description and Composition of the Drug Product .....</b>	<b>13</b>
<b>P.2 Pharmaceutical Development .....</b>	<b>13</b>
P.2.1 Components of the Drug Product.....	13
P.2.1.1 Drug Substance .....	13
P.2.1.2 Excipients .....	14



P.2.2 Drug Product .....	14
P.2.2.1 Formulation Development .....	14
P.2.2.2 Overages .....	15
P.2.2.3 Physicochemical and Biological Properties .....	15
P.2.3 Manufacturing Process Development.....	15
P.2.4 Container Closure System .....	16
P.2.5 Microbiological Attributes .....	16
P.2.6 Compatibility.....	16
<b>P.3 Manufacture.....</b>	<b>17</b>
P.3.1 Manufacturers.....	17
P.3.2 Batch Formula .....	18
P.3.3 Description of Manufacturing Process and Process Controls.....	19
P.3.4 Controls of Critical Steps and Intermediates .....	22
P.3.5 Process Validation and/or Evaluation.....	22
<b>P.4 Control of Excipients.....</b>	<b>23</b>
P.4.1 Specifications .....	23
P.4.2 Analytical Procedures.....	23
P.4.3 Validation of Analytical Procedures.....	23
P.4.4 Justification of Specifications.....	23
P.4.5 Excipients of Human or Animal Origin .....	23
P.4.6 Novel Excipients .....	23
<b>P.5 Control of Drug Product.....</b>	<b>23</b>
P.5.1 Specification(s).....	23
P.5.2 Analytical Procedures.....	25
P.5.3 Validation of Analytical Procedures.....	29
P.5.4 Batch Analyses .....	32
P.5.5 Characterization of Impurities .....	33
P.5.6 Justification of Specification(s).....	34
<b>P.6 Reference Standards or Materials.....</b>	<b>36</b>
<b>P.7 Container Closure System .....</b>	<b>36</b>
<b>P.8 Stability.....</b>	<b>37</b>
P.8.1 Stability Summary and Conclusion.....	37



P.8.2 Postapproval Stability Protocol and Stability Commitment..... 38

P.8.3 Stability Data ..... 39

**A APPENDICES .....41**

A.1 Facilities and Equipment (biotech only) .....41

A.2 Adventitious Agents Safety Evaluation .....41

A.3 Novel Excipients .....41

**R REGIONAL INFORMATION.....41**

R1 Executed Batch Records .....41

R2 Comparability Protocols .....41

R3 Methods Validation Package .....41

**II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1 .....43**

**A. Labeling & Package Insert.....43**

**B. Environmental Assessment Or Claim Of Categorical Exclusion .....43**

**III. LIST OF DEFICIENCIES TO BE COMMUNICATED .....44**

**IV. MISCELLANEOUS .....45**

Attachment 1. Comparison of Echinocandin Structures..... 45



# Chemistry Review Data Sheet

1. NDA 21-632

2. REVIEW #: 1 (Drug Product)

See Chemistry Review #1 (Drug Substance) prepared by Dr. Balajee Shanmugam for drug substance CMC.

3. REVIEW DATE: 05-MAR-2004

4. REVIEWER: Mark R. Seggel, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original NDA

25-APR-2003

BC (info for Methods Validation Package)

25-NOV-2003

BC (product quality microbiology update)

14-JAN-2004

BC (drug substance update)

30-JAN-2004

BC (stability update)

13-FEB-2004

BC (drug substance and drug product updates)

24-FEB-2004

BC (drug substance and drug product updates)

03-MAR-2004



## Chemistry Review Data Sheet

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Vicuron Pharmaceuticals Inc.  
Address: 455 South Gulph Road  
King of Prussia, PA 19406  
Representative: Harriette L. Nadler, PhD  
Senior Director, Regulatory Affairs  
Telephone: 610-491-2211

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:             <sup>TM</sup>  
b) Non-Proprietary Name (USAN): anidulafungin  
c) Code Name/# (ONDC only): VER002; LY303366;  
d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

## 10. PHARMACOL. CATEGORY: Systemic antifungal

## 11. DOSAGE FORM: Lyophilized powder for injection

## 12. STRENGTH/POTENCY: 50 mg/vial

## 13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note22]:

SPOTS product – Form Completed

Not a SPOTS product

## Chemistry Review Data Sheet

**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

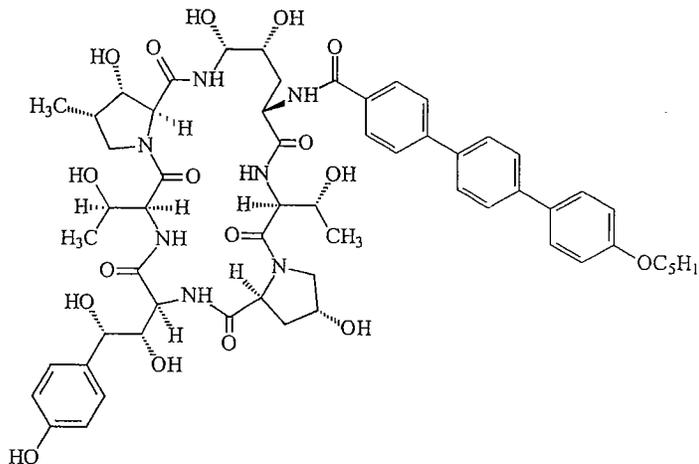
Echinocandin B, 1-[(4R,5R)-4,5-dihydroxy-*N*<sup>2</sup>-[[4''-(pentyloxy)[1,1',:4',1''-terphenyl]-4-yl]carbonyl]-L-ornithine]-

(4R,5R)-4,5-Dihydroxy-*N*<sup>2</sup>-[[4''-(pentyloxy)-p-terphenyl-4-yl]carbonyl]-L-ornithyl-L-threonyl-*trans*-4-hydroxy-L-prolyl-(*S*)-4-hydroxy-(p-hydroxyphenyl)-L-threonyl-L-threonyl-(3*S*,4*S*)-3-hydroxy-4-methyl-L-proline cyclic (6→1)-peptide

Molecular formula: C<sub>58</sub>H<sub>73</sub>N<sub>7</sub>O<sub>17</sub>

Molecular weight: 1140.27

CAS: 166663-25-8


**17. RELATED/SUPPORTING DOCUMENTS:**
**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	3, 4	Adequate	12-FEB-2003	-
[redacted]	III	[redacted]	[redacted]	3, 4	Adequate	06-AUG-2003	-

\*The





# The Chemistry Review for NDA 21-632

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application as amended is recommended for approval from the chemistry, manufacturing and controls perspective.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no recommendations for Phase 4 CMC commitments. The applicant will continue to monitor the stability of the drug substance and drug product. The applicant will also re-evaluate the drug substance and drug product specifications after the manufacture of  $\infty$  commercial batches of each.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is a lyophilized sterile solid containing 50 mg of the antifungal agent anidulafungin. The product is reconstituted and diluted prior to intravenous infusion. A 20% (w/w) ethanol diluent is provided for reconstituting the lyophilized product. The commercial package will contain two 15 mL vials. One vial contains 50 mg of anidulafungin and the second contains the diluent used for reconstituting the drug product. The manufacture of the drug product is straightforward. Common, compendial-grade excipients are used and include fructose, mannitol, tartaric acid, polysorbate 80, and sodium hydroxide and/or hydrochloric acid to adjust the pH. The formulation is  $\left[ \begin{array}{l} \text{ } \\ \text{ } \end{array} \right]$  and lyophilized. The identity, strength, quality and purity of the drug product are assured by release testing appropriate for a product for intravenous administration. The drug product exhibits good stability at 25°C/60% RH. The diluent is simply a 20% aqueous ethanol solution that has been  $\left[ \begin{array}{l} \text{ } \\ \text{ } \end{array} \right]$

Anidulafungin is a semisynthetic antifungal lipopeptide (cyclic hexapeptide with lipophilic acyl side chain) derived from echinocandin B (see Attachment 1 for the structure of echinocandin B and related compounds). It has activity against pathogenic fungi including *Candida* spp. The echinocandins, and structurally related pneumocandins, inhibit the enzyme  $\beta$ -1,3-D-glucan synthetase.  $\beta$ -(1,3)-D-Glucan, a

**Executive Summary Section**

polymer of glucose, is an integral component of the fungal cell wall. The drug substance is insoluble in water and slightly soluble in ethanol. It has good chemical stability, but the recommended storage condition is  $2-8^{\circ}\text{C}$ . The identity, strength, quality and purity of the drug substance as assured by appropriate stability-indicating tests.

**B. Description of How the Drug Product is Intended to be Used**

Anidulafungin for injection is indicated for the treatment of esophageal candidiasis. The intended dosing regimen is a 100-mg loading dose followed by a 50-mg daily maintenance dose for the duration of treatment. The lyophilized drug product requires two dilutions prior to infusion: dilution with the 20% (w/w) ethanol/water diluent and subsequent dilution with either 5% Dextrose Injection USP (D5W) or 0.9% Sodium Chloride Injection USP. The final concentration of the infusion solution is 0.5 mg/mL.

The stability studies support an expiration dating period of 30 months for product stored at  $25^{\circ}\text{C}/60\% \text{RH}$ . The reconstituted solution is stable for up to 24 hours while the infusion solution is stable for up to 24 hours. However, the reconstituted solution should be used within 24 hours of preparation to insure microbiological quality.

**C. Basis for Approvability or Not-Approval Recommendation**

The physicochemical properties of the drug substance have been adequately characterized. The manufacturing process is adequately described. Suitable controls for the drug substance have been established. The stability of the drug substance has also been adequately characterized and appropriate storage conditions established.

The components and composition of the drug product have been adequately specified. The inactive ingredients are commonly used in this dosage form and are of suitable quality. The manufacturing process has been adequately described.

Additional details regarding the manufacture of the drug substance have been provided by the applicant as requested. All issues regarding the drug substance and drug product specifications have been adequately negotiated with the applicant. The applicant will continue to monitor the stability of the drug substance and drug product. The applicant will also re-evaluate the drug substance and drug product specifications after the manufacture of commercial batches of each.

The manufacturing and testing facilities have acceptable cGMP status and the Office of Compliance has issued an Overall Recommendation of Acceptable for the NDA.



### III. Administrative

#### A. Reviewer's Signature

{see Electronic Signature Page}

#### B. Endorsement Block

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

#### C. CC Block

34 Page(s) Withheld



\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(4) Draft Labeling

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

/s/  
-----

Mark Seggel  
5/3/04 12:54:20 PM  
CHEMIST  
N21-632

Norman Schmuff  
5/4/04 06:13:04 AM  
CHEMIST

**NDA 21-632**

**Anidulafungin Infusion**

**Vicuron Pharmaceuticals Inc**

**Balajee Shanmugam**

**HFD-590**

**Division of Special Pathogens and Immunologic Drug  
Products**



# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>3</b>
<b>The Executive Summary .....</b>	<b>6</b>
See Dr. Mark Seggel's review # 1 DP.....	6
<b>Chemistry Assessment .....</b>	<b>7</b>
<b>I. Review Of Common Technical Document-Quality (CTD-Q) Module 3.2: Body Of Data.....</b>	<b>7</b>
<b>S DRUG SUBSTANCE .....</b>	<b>7</b>
S.1 General Information .....	7
S.1.1 Nomenclature.....	7
S.1.2 Structure.....	7
S.1.3 General Properties.....	8
S.2 Manufacture .....	8
S.2.1 Manufacturers .....	8
S.2.2 Description of Manufacturing Process and Process Controls .....	9
S.2.3 Control of Materials .....	30
S.2.4 Controls of Critical Steps and Intermediates.....	32
S.2.5 Process Validation and/or Evaluation .....	33
S.2.6 Manufacturing Process Development.....	34
S.3 Characterization .....	35
S.3.1 Elucidation of Structure and other Characteristics .....	35
S.3.2 Impurities .....	37
S.4 Control of Drug Substance .....	44
S.4.1 Specification.....	44
S.4.2 Analytical Procedures .....	45
S.4.3 Validation of Analytical Procedures .....	48
S.4.4 Batch Analyses.....	53
S.4.5 Justification of Specification.....	57
S.5 Reference Standards or Materials.....	59
S.6 Container Closure System.....	61
S.7 Stability .....	61
S.7.1 Stability Summary and Conclusions .....	62
S.7.2 Postapproval Stability Protocol and Stability Commitment .....	65
S.7.3 Stability Data.....	66



# Chemistry Review Data Sheet

1. NDA 21-632
2. REVIEW # 1 DS (drug substance, for drug product see Dr. Mark Seggel's review # 1 DP)
3. REVIEW DATE:
4. REVIEWER: Balajee Shanmugam
5. PREVIOUS DOCUMENTS: N/A

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed  
Original submission

Document Date  
04-25-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Vicuron Pharmaceuticals

Address: 455 South Gulph Road, King of Prussia, PA 19406

Representative: Harriette L. Nadler, Ph.D.

Telephone: 610-491-2211



## CHEMISTRY REVIEW



### Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN): Anidulafungin
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)

10. PHARMACOL. CATEGORY: Antifungal

11. DOSAGE FORM: Infusion

12. STRENGTH/POTENCY: 50 mg

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 1-[(4R,5R)-4,5-Dihydroxy-N(2)-[[4''-(pentyloxy)[1,1':4',1''-terphenyl]-4-yl]carbonyl]-L-ornithine]echinocandin B

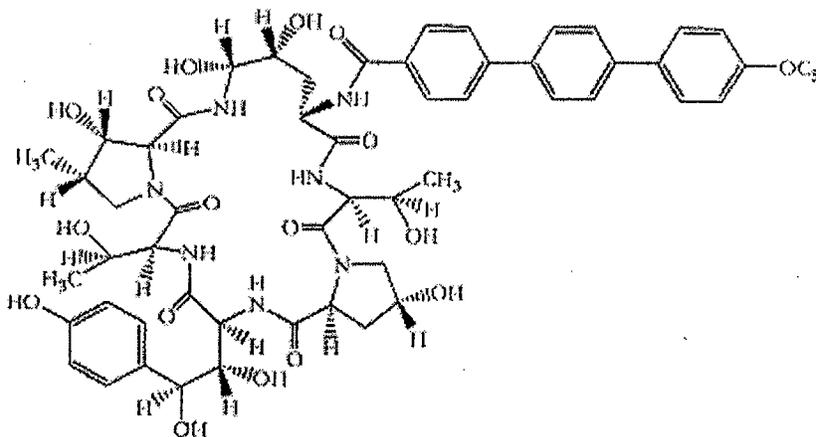


# CHEMISTRY REVIEW



## Executive Summary Section

### Structure of Anidulafungin



Molecular Formula:  $C_{58}H_{73}N_7O_{17}$

Molecular Weight: 1140.3

## 17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS

For DP DMF's see review #1 DP.

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



# CHEMISTRY REVIEW



## Executive Summary Section

### 18. STATUS:

**ONDC: See DP review # 1 DP**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES			
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA			
Microbiology			

### *The Executive Summary*

See Dr. Mark Seggel's review # 1 DP

Appears This Way  
On Original

63 Page(s) Withheld



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

       § 552(b)(5) Deliberative Process

       § 552(b)(4) Draft Labeling

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

/s/

-----  
Balajee Shanmugam  
4/28/04 04:24:03 PM  
CHEMIST

Norman Schmuff  
4/29/04 01:13:26 PM  
CHEMIST