

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-630

CHEMISTRY REVIEW(S)



NDA 21-630

VFEND[®] (voriconazole) Powder for Oral Suspension

Pfizer Global Research & Development

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Immunologic Drug Products**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	7
The Executive Summary	11
I. Recommendations	11
A. Recommendation and Conclusion on Approvability	11
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	11
II. Summary of Chemistry Assessments.....	11
A. Description of the Drug Product(s) and Drug Substance(s)	11
B. Description of How the Drug Product is Intended to be Used.....	12
C. Basis for Approvability or Not-Approval Recommendation.....	12
III. Administrative.....	13
A. Reviewer's Signature.....	13
B. Endorsement Block.....	13
C. CC Block	13
Chemistry Assessment	14
I. Review Of Common Technical Document-Quality (CTD-Q) Module 3.2: Body Of Data.....	14
S DRUG SUBSTANCE.....	14
S.1 General Information.....	14
S.1.1 Nomenclature.....	14
S.1.2 Structure	14
S 1.3 General Properties.....	14
S.2 Manufacture.....	14
S.2.1 Manufacturers	14
S.2.2 Description of Manufacturing Process and Process Controls	15
S.2.3 Control of Materials	15
S.2.4 Controls of Critical Steps and Intermediates.....	15

Chemistry Review Data Sheet

S.2.5	Process Validation and/or Evaluation	15
S.2.6	Manufacturing Process Development	15
S.3	Characterization	15
S.3.1	Elucidation of Structure and other Characteristics	15
S.3.2	Impurities	15
S.4	Control of Drug Substance.....	15
S.4.1	Specification.....	16
S.4.2	Analytical Procedures	16
S.4.3	Validation of Analytical Procedures	16
S.4.4	Batch Analyses.....	16
S.4.5	Justification of Specification.....	17
S.5	Reference Standards or Materials	17
S.6	Container Closure System.....	17
S.7	Stability	17
S.7.1	Stability Summary and Conclusions	17
S.7.2	Post-Approval Stability Protocol and Stability Commitment	17
S.7.3	Stability Data.....	17
P	DRUG PRODUCT	17
P.1	Description and Composition of the Drug Product - Acceptable	17
P.2	Pharmaceutical Development	18
P.2.1	Components of the Drug Product.....	18
P.2.1.1	Drug Substance.....	18
P.2.1.1.1	Solubility.....	18
P.2.1.1.2	Particle Size Distribution	19
P.2.1.1.3	Polymorphs, hydrates and Solvates	23
P.2.1.1.4	Excipient Compatibility	23
P.2.1.2	Excipients.....	23
P.2.2	Drug Product	23
P.2.2.1	Formulation Development	23
P.2.2.2	Overages	27
P.2.2.3	Physicochemical and Biological Properties.....	27
P.2.3	Manufacturing Process Development	30
P.2.3.1	Scale-up and Manufacturing Experience	33
P.2.4	Container Closure System.....	36

Chemistry Review Data Sheet

P.2.4.1	Description.....	36
P.2.4.2	Suitability.....	36
P.2.4.2.1	Protection.....	36
P.2.4.2.2	Compatibility.....	37
P.2.4.2.4	Performance.....	39
P.2.5	Microbiological Attributes.....	40
P.2.6	Compatibility.....	42
P.2. Attachment A		42
P.2 Attachment B		43
P.3 Manufacture		44
P.3.1	Manufacturers - Acceptable.....	44
P.3.2	Batch Formula - Acceptable.....	45
P.3.3	Description of Manufacturing Process and Process Controls - Acceptable.....	46
P.3.3.1	Manufacturing Process Flow Chart.....	46
P.3.3.2	Manufacturing Process Description.....	46
P.3.3.3	Packaging Procedures.....	46
P.3.4	Controls of Critical Steps and Intermediates - Acceptable.....	47
P.3.5	Process Validation and/or Evaluation.....	49
P.4 Control of Excipients - Acceptable		49
P.4.1	Specifications - Acceptable.....	49
P.4.1.1	Specifications for Compendial Excipients.....	49
P.4.1.2	Specifications for Non-Compendial Excipients.....	50
P.4.2	Analytical Procedures.....	50
P.4.2.1	Analytical Procedures for Compendial Excipients.....	50
P.4.2.2	Analytical Procedures for Non-Compendial Excipients.....	50
P.4.3	Validation of Analytical Procedures.....	51
P.4.3.1	Validation of Analytical Procedures for Compendial Excipients.....	51
P.4.3.2	Validation of Analytical Procedures for Non-Compendial Excipients.....	51
P.4.4	Justification of Specifications.....	51
P.4.4.1	Justification of Specifications for Compendial Excipients.....	51
P.4.4.2	Justification of Specifications for Non-Compendial Excipients.....	51
P.4.5	Excipients of Human or Animal Origin.....	53
P.4.5.1	Compendial Excipients of Human or Animal Origin.....	53
P.4.5.1	Non-Compendial Excipients of Human or Animal Origin.....	54

Chemistry Review Data Sheet

P.4.6	Novel Excipients	54
P.5	Control of Drug Product - Acceptable	54
P.5.1	Specification.....	54
P.5.2	Analytical Procedures	55
P.5.3	Validation of Analytical Procedures	65
P.5.4	Batch Analyses.....	81
P.5.5	Characterization of Impurities.....	81
P.5.6	Justification of Specification(s).....	85
P.6	Reference Standards or Materials - Acceptable.....	93
P.7	Container Closure System - Acceptable	93
P.7.1	Description	93
P.7.2	Packaging Component Descriptions	94
P.7.3	Quality Control.....	97
P.7.4	Analytical Methods for Packaging Components.....	98
P.7.5	DMF References	100
P.8	Stability - Acceptable.....	100
P.8.1	Stability Summary and Conclusion.....	100
P.8.1.1	Drug Product Stress Testing Studies.....	103
P.8.1.2	Stability Protocols for Voriconazole Powder for Oral Suspension.....	104
P.8.1.3	Results of Formal and Supporting Stability Studies	106
P.8.1.4	Detailed Review.....	108
P.8.1.5	Additional Studies.....	117
P.8.1.6	Expiry Dating.....	119
P.8.2	Post-Approval Stability Protocol and Stability Commitment	119
P.8.3	Stability Data.....	120
P.8.3.1	Formal and Supporting Stability Programs.....	120
A	APPENDICES	121
A.1	Facilities and Equipment (biotech only) - Acceptable	121
A.2	Adventitious Agents Safety Evaluation - Acceptable	121
A.3	Novel Excipients	122
R	REGIONAL INFORMATION - Acceptable.....	122
R.1.1	Introduction	122
R.1.2	Executed Batch Records.....	122



CHEMISTRY REVIEW



Chemistry Review Data Sheet

II. Review Of Common Technical Document-Quality (CTD-Q) Module 1	123
A. Labeling & Package Insert - Acceptable	123
B. Environmental Assessment Or Claim Of Categorical Exclusion - Acceptable	124
III. List Of Deficiencies To Be Communicated.....	125



Chemistry Review Data Sheet

1. NDA 21-630
2. REVIEW #: 1
3. REVIEW DATE: 19-NOV-2003
4. REVIEWER: Gene W. Holbert, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment (BC)

Amendment (BC)

Document Date

14-MAR-2003

14-NOV-2003

25-NOV-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer Global Research & Development

Worldwide Regulatory Affairs

Address: 50 Pequot Avenue
New London, CT 06320

Representative: Maureen H. Garvey, Ph.D.

Telephone: 212-733-5688

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: VFEND®
- b) Non-Proprietary Name (USAN): voriconazole
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Antifungal

11. DOSAGE FORM: Powder for Oral Suspension

12. STRENGTH/POTENCY: 40 mg/mL when constituted

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):☐ SPOTS product – Form Completed☒ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1H-1,2,4-triazol-1-yl)-2-butanol



Molecular Formula: C₁₆H₁₄F₃N₅O Molecular Weight: 349.3 CAS #: 137234-62-9

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
				1	Adequate	21-OCT-2003	
				3	Adequate	19-DEC-2000	
				4, 6, 7			Several other containers from this supplier have been found adequate as well as the
				4	N/A		has been reviewed.
				3	Adequate	23-MAR-1999	
				3	Adequate	30-MAY-2003	
				3	Adequate	01-MAY-2003	

¹ 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")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-266	VFEND® Tablets
NDA	21-267	VFEND® Injection
IND	66,410	VFEND® powder for Oral Suspension



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	25-APR-2003	
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
DDMAC	Acceptable	25-SEP-2003	Iris Masucci, Pharm. D., BCPS
EA			
Microbiology			

**Appears This Way
On Original**

The Chemistry Review for NDA 21-630

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, this NDA is recommended for approval.

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

N/A

II. Summary of Chemistry Assessments

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

The active pharmaceutical ingredient (API), voriconazole (UK-109,496) is another member of the triazole series of synthetic antifungal agents, and has demonstrated *in vitro* fungicidal activity against *Aspergillus* spp, *Fusarium* spp and *Scedosporium apiospermum* and a range of filamentous fungi. Voriconazole functions by specifically inhibiting fungal cytochrome P-450-dependent 14- α sterol demethylation, an essential step in the biosynthesis of ergosterol. Voriconazole drug substance is an enantiomerically pure, single diastereomer (2*R*,3*S*), and is present as the free base.

VFEND® (voriconazole) Tablets (NDA 21-266) and VFEND® IV (voriconazole) for Injection (NDA 21-267) are currently approved products. Voriconazole for Oral Suspension was developed to provide an oral formulation for those patients for whom tablets are not an appropriate dosage form.

For the majority of chemistry, manufacturing and controls information regarding the drug substance, reference is made to NDA 21-266. The same drug substance is used for both the tablet and the suspension formulations. The analytical methods and acceptance criteria remain the same. The drug substance will be stored at the long-term condition of 25°C/40% RH with a retest period of

VFEND® (voriconazole) for Oral Suspension is a white to off-white orange flavored powder containing 40 mg voriconazole/mL after constitution with 46 mL of water. The formulation also contains Sucrose, Colloidal Silicon Dioxide, Titanium Dioxide,

Executive Summary Section

Xanthan Gum, Sodium Citrate Dihydrate, Citric Acid (anhydrous), Sodium Benzoate as a preservative and Natural Orange Flavor.

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

Therapy is initiated with the specified loading dose regimen of VFEND® I.V. to achieve plasma concentrations on Day 1 that are close to steady state. For treatment of adults with invasive aspergillosis and infections caused by *Fusarium* spp. and *Scedosporium apiospermum*, the recommended loading dose is 6 mg/kg VFEND® I.V. every 12 hours for two doses followed by a maintenance dose of 4 mg/kg VFEND® I.V. every 12 hours.

Once able to tolerate oral medication, the patient may be switched to either VFEND Tablets or VFEND for Oral Suspension. Patients weighing 40 kg or more receive either 200 mg (5 mL of suspension or one 200 mg tablet) every 12 hours. For patients weighing less than 40 kg, the dose is 100 mg (2.5 mL suspension or two 50 mg tablets) every 12 hours. The oral maintenance may be increased by 50% if the response is inadequate.

In patients unable to tolerate treatment, the I.V. maintenance dose may be reduced to 3 mg/kg every 12 hours and the oral dose decreased in 50 mg steps to a minimum of 200 mg (100 mg depending on weight) every 12 hours.

VFEND Oral Suspension should be taken at least one hour before or one hour after a meal.

The sponsor proposed 18-month expiration date for the drug product when stored refrigerated at 2-8°C. After constitution, the suspension is to be stored at controlled room temperature with an expiration date of 14 days. The data provided is adequate to support the proposed expiration dating.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments ultimately provided adequate information on the chemistry, manufacturing and controls for the production of VFEND® (voriconazole) for Oral Suspension. The drug substance specification is identical to



CHEMISTRY REVIEW



Executive Summary Section

that for voriconazole tablets. For the product, the specification is comparable in terms of assay and impurities to the tablets as well. Minor deficiencies were identified.

As amended, all methods and acceptance criteria were found acceptable for the drug product.

DDMAC has found the labeling generally acceptable with minor comments only.

III. Administrative

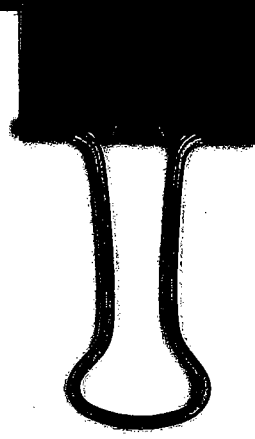
A. Reviewer's Signature

Signed electronically in DFS

B. Endorsement Block

Chemist: Gene W. Holbert, Ph.D./Date: 19-NOV-2003
Chemistry Team Leader: Norman R. Schmuff, Ph.D./Date
Project Manager: Rebecca Saville, Pharm.D./Date

C. CC Block



115 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) 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/

Gene Holbert
12/10/03 05:44:30 PM
CHEMIST

Norman Schmuff
12/11/03 12:46:18 PM
CHEMIST