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

Gene W. Holbert, Ph.D.
Division of Special Pathogen and
Immunologic Drug Products

Table of Contents

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	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	14-MAR-2003
Amendment (BC)	14-NOV-2003
Amendment (BC)	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

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

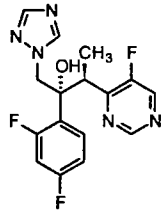
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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

    _X_ Not a SPOTS product

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



Molecular Formula: $C_{16}H_{14}F_3N_5O$ **Molecular Weight:** 349.3 **CAS #:** 137234-62-9

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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

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 [redacted]

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,

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

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

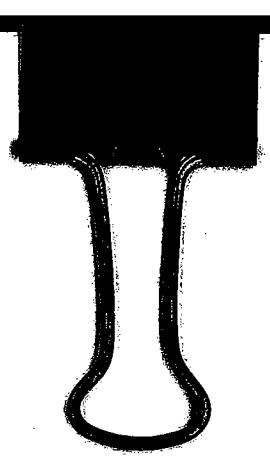
A. Reviewer's Signature

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

Withheld Track Number: Chemistry- 1

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