CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208562Orig1s000

SUMMARY REVIEW

Division Director Decisional Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Decisional Memo
NDA #	208562
Applicant Name	Xellia Pharmaceuticals ApS
Date of Re-submission (Class I)	January 9, 2017
PDUFA Goal Date	March 9, 2017
Established (USAN) Name	Voriconazole for Injection
Dosage Forms / Strength	Powder for Injection, 200 mg/vial
Proposed Indications	Invasive aspergillosis; Candidemia in nonneutropenic patients and disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds; Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species including *Fusarium solani*, in patients intolerant of, or refractory to other therapy
Recommended Action:	Approval

1.0 Introduction

NDA 208562 was submitted by Xellia Pharmaceuticals ApS under Section 505(b)(2) of the Food Drug and Cosmetic Act. The Applicant refers to two listed drugs: NDA 21267 (VFEND, Pfizer) and NDA 20966 (Sporanox, Janssen Pharmaceuticals). The proposed drug product, Voriconazole for Injection, 200 mg/vial, is a new formulation of voriconazole lyophilized powder for injection, and differs from VFEND in that it contains (b) (4) hydroxypropyl β-cyclodextrin (HPβCD) instead of sulfobutylether β-cyclodextrin (SBEβCD). NDA 20966 is currently not marketed and was not withdrawn for safety or efficacy reasons (FR notice dated June 08, 2011).

This NDA received a tentative approval on May 24, 2016, due to outstanding patent issues. As the patent issues have been resolved, the NDA was resubmitted. In addition to minor CMC changes, labeling updates are provided in this resubmission.

This memo will only focus on aspects of the NDA relevant to this resubmission. All reviewers had recommended approval of the NDA during the previous review cycle. Please refer to the discipline specific reviews and the cross-discipline team leader (CDTL) memos for the original NDA and the resubmission for further details.

2.0 Product Quality

In this resubmission, the Applicant provided updates regarding the excipient HPβCD and the container closure system specifications. In addition, a description of the manufacturing process was updated to include process validation recommendations resulting from the manufacture of three commercial scale batches. These updates were reviewed by the Office of Pharmaceutical Quality (OPQ) and found to be acceptable. The Office of Process and Facilities (OPF) has provided an overall recommendation of "Approve". The OPQ review team recommends approval of the NDA. I agree with their assessment.

3.0 Labeling

Labeling recommendations provided by the review team, including the Office of Prescription Drug Promotion and the Division of Medication Error Prevention and Analysis have been incorporated in the package insert and vial and carton labels.

4.0 Other Regulatory Issues

The following unexpired patents are listed in the Orange Book for the listed drugs in this NDA:

VFEND (NDA 21267): US Patent No. 6,632,803 - Expiry Date: June 2, 2018

The Applicant has submitted a Paragraph IV Certification regarding the above patent and certified that notices regarding the Paragraph IV certification were delivered to the holders of the patent and the NDA (Pfizer Inc. and PF Prism C.V.).

SPORANOX (NDA 20966): US Patent No. 6,407,079 - Expiry Date: June 18, 2019

The Applicant has submitted Paragraph IV Certification for the above patent. On June 29, 2016, Janssen filed suit against Xellia in the U.S. District Court for the District of Delaware alleging infringement of U.S. Patent No. 6,407,079 and resulting in a 30-month stay of approval. On December 22, 2016, the court terminated the 30-month stay of approval for NDA 208562.

5.0 Recommended Regulatory Action

I agree with the recommendations made by the review team and the CDTL that NDA 208562 be approved.

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/s/

SUMATHI NAMBIAR
03/09/2017

Division Director Decisional Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Decisional Memo
NDA #	208562
Applicant Name	Xellia Pharmaceuticals ApS
Date of Submission	July 24, 2015
PDUFA Goal Date	May 24, 2016
Established (USAN) Name	Voriconazole for Injection
Dosage Forms / Strength	Powder for injection, 200 mg/vial
Proposed Indications	Invasive aspergillosis; Candidemia in nonneutropenic patients and disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds; Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species including *Fusarium solani*, in patients intolerant of, or refractory to other therapy
Recommended Action:	Tentative Approval

Material Reviewed/Consulted Action Package including:	**Names of Discipline Reviewers**
Product Quality Application Technical Lead	Dorota Matecka PhD
Cross-Discipline Team Leader Review	Dorota Matecka PhD
Medical Officer Review	Caroline Jjingo MD MPH
Clinical Microbiology Review	Shukal Bala, PhD
Clinical Pharmacology Review	Grace (Zhixia) Yan PhD
Pharmacology-Toxicology Review	Owen McMaster PhD
Division of Medication Error Prevention and Analysis	Sevan Kolejian Pharm D

1.0 Introduction

NDA 208562 was submitted by Xellia Pharmaceuticals ApS under Section 505(b)(2) of the Food Drug and Cosmetic Act. The Applicant refers to two listed drugs: NDA 21267 (VFEND, Pfizer) and NDA 20966 (Sporanox, Janssen Pharmaceuticals). The proposed drug product, Voriconazole for Injection, 200 mg/vial, is a new formulation of voriconazole lyophilized powder for injection, and differs from VFEND in that it contains (b) (4) hydroxypropyl β-cyclodextrin (HPβCD) instead of sulfobutylether β-cyclodextrin (SBEβCD). NDA 20966 is currently not marketed and was not withdrawn for safety or efficacy reasons (FR notice dated

June 08, 2011). No clinical data have been submitted in this NDA as the Applicant is relying on FDA's findings of efficacy and safety for VFEND and Sporanox. In view of the similarities between the proposed and listed drugs, the Applicant requested a waiver for conducting in-vivo bioequivalence studies.

2.0 Product Quality

The chemistry manufacturing and controls information for voriconazole drug substance has been provided via reference to DMF Type II (b) (4). DMF (b) (4) has been found to be adequate (review dated January 08, 2015). The proposed drug product contains the same active ingredient in the same amount as VFEND. The (b) (4) (SBEβCD) in VFEND has been replaced with the same amount of a (b) (4) (HPβCD) in the currently proposed formulation.

The drug product is a white to off-white cake or powder which contains 200 mg of voriconazole and 3200 mg HPβCD. The proposed specification (tests, analytical procedures and acceptance criteria) was found acceptable. The proposed drug product is supplied in a glass vial with a rubber stopper. The overall information provided for the proposed container closure system was found acceptable. Compatibility data of the proposed drug product with drugs listed in the proposed package insert was found adequate. The stability data provided was found acceptable and support an expiration dating of 24 months, stored at 20°C- 25°C (68°-77°F) excursions permitted between 15°C to 30°C (59°F to 86°F).

The Applicant requested a biowaiver in accordance with 21 CFR 320.22(b). The Biopharmaceutics Reviewer, Dr. Gieser, notes that the in vitro comparability experiments conducted by the Applicant showed that the voriconazole (b) (4) HPβCD is similar to SBEβCD and that the (b) (4) used. Dr. Gieser also notes that the pH range of the Applicant's proposed voriconazole drug product upon reconstitution, the osmolality/osmolarity of the infusion solution upon reconstitution and dilution, and the in vitro antifungal activity are comparable to those of VFEND. Therefore, Dr. Gieser concluded that the overall information provided in the NDA supports the biowaiver request, and the biowaiver request is granted, per 21 CFR 320.24(b)(5).

Information provided for the proposed drug product from the product quality microbiology perspective (i.e., (b) (4) was found acceptable.

The drug substance manufacturing sites are (b) (4) The drug product facilities include (b) (4)

(b) (4) All manufacturing and testing facilities for this NDA have been found acceptable by the Office of Process and Facilities (OPF) and an overall "approve" recommendation has been provided.

As noted in the review dated May 24, 2016, the Office of Pharmaceutical Quality review team recommends approval of this NDA. I agree with the team's assessment.

3.0 Clinical Pharmacology

Grace (Zhixia) Yan, PhD, is the clinical pharmacology reviewer for this NDA. No new clinical pharmacology studies were conducted by the Applicant. Dr. Yan did not agree with the Applicant's proposal to (b) (4) and has provided revised labeling language to state that in patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min), accumulation of HPβCD can occur. Hence, serum creatinine should be closely monitored in these patients and if there is an increase in serum creatinine, alternate antifungal therapy should be considered unless an assessment of the benefit/risk justifies the continued use of intravenous voriconazole. This labeling recommendation was based on the labeling for Sporanox (itraconazole) and VFEND (voriconazole), the listed drugs for this NDA and the published literature.

Dr. Yan notes that the clinical pharmacology information provided by the Applicant is acceptable and supports approval of the NDA.

Philip Colangelo, PharmD, PhD, clinical pharmacology team leader, has provided an addendum dated May 24, 2016. In the addendum Dr. Colangelo notes that the information from the (b) (4) and also noted in the review by Dr. Yan (b) (4).

4.0 Clinical Microbiology

The Applicant performed in vitro studies against quality control strains of three Candida species to assess if the new formulation had any impact on the antifungal activity of voriconazole. In Dr. Bala's assessment there was no impact on the activity of voriconazole. Labeling recommendations provided by Dr. Bala have been incorporated in labeling. Dr. Bala recommends approval of the NDA.

5.0 Pharmacology-Toxicology

Owen McMaster, PhD, is the pharmacology-toxicology reviewer for this NDA. No new pharmacology-toxicology data were submitted in this NDA. Dr. McMaster notes that there are

no safety concerns with the substitution of SBEβCD with HPβCD and recommends approval of this NDA.

6.0 Clinical Efficacy/Safety

Caroline Jjingo, MD MPH, is the clinical reviewer for this NDA. No new clinical data were submitted in this NDA. Dr. Jjingo performed a review of the literature and no new safety information was identified. The Applicant performed a review of the literature and a search of the FDA Adverse Event Reporting System. No new safety signals were identified that required a labeling revision. Dr. Jjingo provided labeling recommendations, including removal of the (b) (4)
Dr. Jjingo recommends approval of this NDA.

In an addendum, dated May 24, 2016, Dr. Jjingo notes the amendments submitted by the Applicant stating that they are relying on Sporanox as one of the listed drugs and that they are relying on the vitro test conducted by Xellia to support the biowaiver request are acceptable.

Cheryl Dixon, PhD, is the statistical reviewer for this NDA. No new clinical data were submitted in this NDA. Dr. Dixon agrees with the removal of the (b) (4) from the Clinical Studies section of the package insert.

7.0 Labeling

Labeling recommendations provided by Adam George, PharmD, from the Office of Prescription Drug Promotion have been incorporated in labeling. Sevan Kolejian, PharmD, from the Division of Medication Error Prevention and Analysis provided labeling revisions to the package insert, container, and carton. These revisions have been incorporated in labeling.

8.0 Pediatrics

Under the Pediatric Research and Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless the requirement is waived, deferred or inapplicable. As none of these criteria are applicable, this NDA is exempt from PREA requirements.

9.0 Other Regulatory Issues

In the NDA submission, the Applicant provided the following patent certifications for NDA 21267:

Paragraph IV certification for US patent number 5,567,817, expiration date May 24, 2016

Paragraph IV certification for US patent number 6,632,803, expiration date June 02, 2018

In an amendment to the NDA, dated May 23, 2016, the Applicant provided Paragraph IV certification for US patent number 6,407,079, for NDA 20966 with an expiration date of June 18, 2019. The Applicant has provided the notices of certification for each patent for which the Applicant has provided paragraph IV certifications and delivery receipts.

10.0 Recommended Regulatory Action

I agree with the recommendations made by the review team and the cross-discipline team leader that NDA 208562 be approved. As one of the listed drugs upon which the application relies is subject to a period of patent and/or exclusivity protection, the NDA will be tentatively approved per 21 CFR 314.105.

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/s/

SUMATHI NAMBIAR
05/24/2016