CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207500Orig1s000 / 207501Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **March 4, 2015**

From: **Yichun Sun, Ph.D.**
Review Chemist
Division of New Drug Products II
Office of New Drug Products

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: **CMC Review #1 of NDA 207500**

Subject: **Final Approval Recommendation for NDA 207500**

At the time when the CMC review #1 was written, resolution of issues on **Labels and Labeling** was pending. Additionally, the Office of Compliance had not issued an overall "Acceptable" recommendation for the facilities involved in this application.

Label/Labeling

The strength expression of the drug product has been quite challenging due to the complexity of the mechanism of the drug substance to release its active moiety, isavuconazole. The drug substance, isavuconazonium sulfate, is a prodrug. The cation, isavuconazonium, contains the active moiety of the drug. The active moiety is released from isavuconazonium through hydrolysis. The conversion pathway from isavuconazonium sulfate (BAL 8557) to the active moiety, isavuconazole (BAL 4815), is shown below:

(b) (4)

The initial strength established name and expression proposed by the applicant are:

CRESEMBA (isavuconazonium sulfate) capsules
[redacted] (b) (4)

After discussions within OPQ (ONDP and LNC), in order to minimize the risk of medication errors and confusion, the following established name and strength are recommended for Cresemba according to LNC chairman, Dr. Richard Lostritto's email dated February 13, 2015.

> *CRESEMBA (isavuconazonium sulfate) capsules, 186 [redacted] (b) (4) mg*
> *Equivalent to 100 mg isavuconazole*

The aforementioned recommendation was discussed with the applicant during the T-con between Division of Anti-Infective Products and the applicant. The T-con was held on February 19, 2015. Additionally, the Division also recommended that [redacted] (b) (4) during the T-con. Therefore, the established name and strength for Cresemba are shown as follows:

> *CRESEMBA (isavuconazonium sulfate) capsules, 186 mg*
> *Equivalent to 100 mg isavuconazole*

On March 4, 2015, the NDA applicant submitted an amendment providing the finalized mock up carton and blister labels. Additionally, the applicant also agreed to all the CMC changes made to the package insert. All the labels/labeling issues are now **satisfactorily resolved.** The CMC sections of the final package insert, and mock up container labels are attached (**Attachment - 1**).

Establishment Evaluation

On March 3, 2015, the office of compliance provided an **Overall Acceptable** recommendation for the facilities involved in the manufacture and test of the drug substance and drug product. The Establishment Evaluation is attached (**Attachment - 2**).

Recommendation:

All pending issues on CMC and Label/Labeling are now satisfactorily resolved for the NDA, and the office of compliance provided an **Overall Acceptable** recommendation for the facilities involved in the manufacture and test of the drug substance and drug product. Therefore, from the ONDP's perspective, this NDA is recommended for **APPROVAL**. An expiration dating period of **30 months** is granted for the drug product of NDA 207500.

Attachment - 1 (CMC Sections of the Finalized Labeling and Labels)

A. Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section

CRESEMBA® (isavuconazonium sulfate) Capsules, for oral administration
Initial U.S. Approval: 2015

DOSAGE FORMS AND STRENGTHS
CRESEMBA capsules contain 186 mg of isavuconazonium sulfate (equivalent to 100 mg of isavuconazole).

Evaluation:

Item	Comments on the Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	The proprietary name and established name are correctly described. **Satisfactory**
Dosage form, route of administration	The dosage form is "Capsules". The administration route is oral. **Satisfactory**
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (201.57(a)(8))	The dosage form is capsules. Each capsule contains 186 mg of isavuconazonium sulfate (equivalent to 100 mg isavuconazole). **Satisfactory**
Whether the drug product is scored	N/A

This section is satisfactory.

(b) "Full Prescribing Information" Section

#3. Dosage Form and Strength

Each CRESEMBA capsule contains 186 mg isavuconazonium sulfate (equivalent to 100 mg of isavuconazole). Capsules are opaque and elongated, and have a Swedish Orange (reddish-brown) body imprinted with the Astellas logo in black ink and a white cap imprinted with "ISA" in black ink.

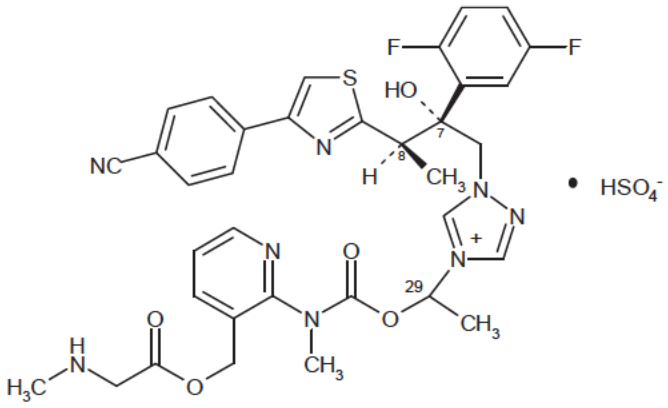
Evaluation:

Item	Comments on the Information Provided in NDA
Available dosage forms and strengths: in metric system	The dosage form is "Capsules". The strength is 186 mg of isavuconazonium sulfate (equivalent to 100 mg isavuconazole). **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	Each capsule contains 186 mg of isavuconazonium sulfate (equivalent to 100 mg isavuconazole). **Satisfactory**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Capsules are opaque and elongated, and have a Swedish Orange (reddish-brown) body imprinted with the Astellas logo in black ink and a white cap imprinted with "ISA" in black ink. **Satisfactory**
Other	NA

This section is satisfactory.

#11. Description

CRESEMBA contains isavuconazonium sulfate, which is the prodrug of isavuconazole, an azole antifungal drug. Isavuconazonium sulfate drug substance is an amorphous, white to yellowish white powder. The chemical name of isavuconazonium sulfate is glycine, N-methyl-, [2-[[[1-[1-[(2R,3R)-3-[4-(4-cyanophenyl)-2-thiazolyl]-2-(2,5-difluorophenyl)-2- hydroxybutyl]-4H-1,2,4-triazolium-4-yl]ethoxy]carbonyl]methylamino]-3-pyridinyl]methyl ester, sulfate (1:1). The empirical formula is $C_{35}H_{35}F_2N_8O_5S \cdot HSO_4$, the molecular weight is 814.84 and the structural formula is:



CRESEMBA (isavuconazonium sulfate) capsules are available for oral administration. Each CRESEMBA capsule contains 186 mg isavuconazonium sulfate, equivalent to 100 mg isavuconazole. The inactive ingredients include magnesium citrate, microcrystalline cellulose, talc, colloidal silicon dioxide, stearic acid, hypromellose, red iron oxide, titanium dioxide, purified water, gellan gum, potassium acetate, disodium edetate, sodium laurylsulfate, shellac, propylene glycol, strong ammonia solution, potassium hydroxide and black iron oxide.

Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name and established name	The proprietary name is CRESEMBA. The established name is correctly described as: isavuconazonium sulfate. **Satisfactory**
Dosage form and route of administration	The dosage form is: "Capsules". The administration route is oral. **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	186 mg isavuconazonium sulfate, equivalent to 100 mg isavuconazole. **Satisfactory**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)).	All inactive ingredients are listed as follows: magnesium citrate, microcrystalline cellulose, talc, colloidal silicon dioxide, stearic acid, hypromellose, red iron oxide, titanium dioxide, purified water, gellan gum, potassium acetate, disodium edetate, sodium laurylsulfate, shellac, propylene glycol, strong ammonia solution, potassium hydroxide and black iron oxide. **Satisfactory**
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	The pharmacological class, antifungal agent, is provided. **Satisfactory**
Chemical name, structural formula, molecular weight	Chemical name structural formula and the molecular weight are correctly described in this section. **Satisfactory**
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	N/A

The "Description" section is satisfactory.

#16. How Supplied/Storage and Handling

CRESEMBA (isavuconazonium sulfate) capsules are available in aluminum blister packs. Each capsule contains 186 mg isavuconazonium sulfate (equivalent to 100 mg of isavuconazole). Capsules are opaque and elongated, and have a

Swedish orange (reddish-brown) body imprinted with the Astellas logo in black ink and a white cap imprinted with "ISA" in black ink.

Store in original container to protect from moisture.

Capsules are packaged in aluminum blister packs, seven (7) capsules per sheet with desiccant. (NDC 0469-0320-14)

Store CRESEMBA capsules at 20°C to 25°C (68°F to 77°F) in the original packaging to protect from moisture. Excursions are permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Evaluation:

Item	**Comments on the Information Provided in NDA**
Strength of dosage form	Strength is correctly described as 186 mg of isavuconazonium sulfate (equivalent to 100 mg of isavuconazole). **Satisfactory**
Available units (e.g., bottles of 100 tablets)	Available units are correctly described as Seven (7) capsules per sheet with desiccant. **Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Capsules are opaque and elongated, and have a Swedish orange (reddish-brown) body imprinted with the Astellas logo in black ink and a white cap imprinted with "ISA" in black ink. **Satisfactory**
Special handling (e.g., protect from light)	Store in original container to protect from moisture. **Satisfactory**
Storage conditions	Storage condition is described as: Store CRESEMBA capsules at 20°C to 25°C (68°F to 77°F) in the original packaging to protect from moisture. Excursions are permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. **Satisfactory**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Stated at the end of the labeling as: Astellas Pharma US, Inc. **Satisfactory**
Other	N/A

The "How Supplied/Storage and Handling" section is satisfactory.

2. Container/carton labels

Immediate container label

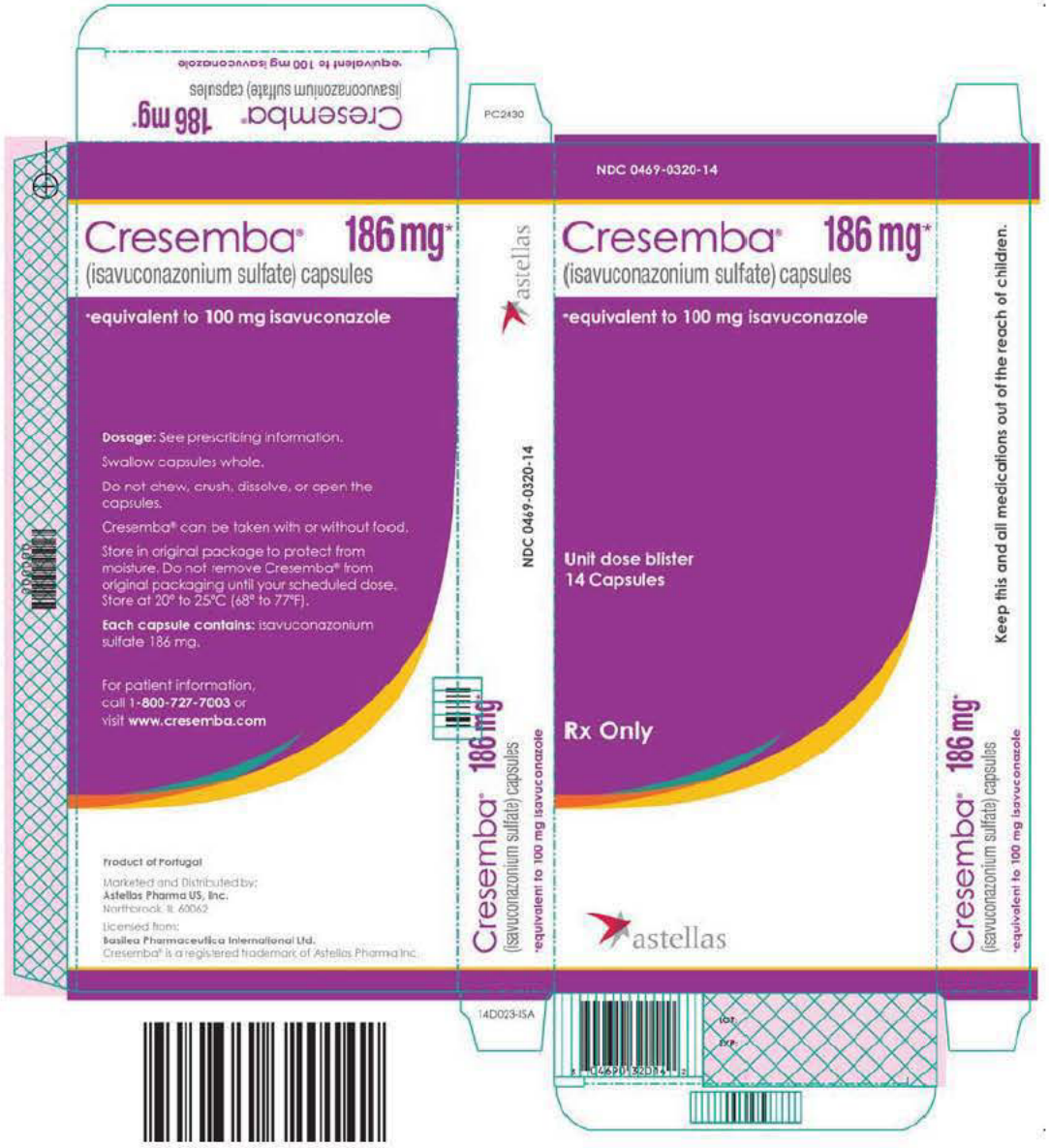
Blister Label

Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name is correctly described. The established name is isavuconazonium sulfate. **Satisfactory**
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength is correctly described as186 mg isavuconazonium sulfate equivalent to 100 mg isavuconazole. **Satisfactory**
"Rx only" displayed prominently on the main panel	The "Rx only" statement is displayed. **Satisfactory**
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number is not indicated. However, it is acceptable as it is requested but not required (21 CFR 207.35(b)(3)(i). **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	A space is allocated for this information. **Satisfactory**
Bar code (21CFR 201.25)	Barcode is indicated. **Satisfactory**
Name of manufacturer/distributor	The name of distributor is described as required per 21CFR 201.1. **Satisfactory**
And others, if space is available	N/A

The blister (unit container) label is satisfactory.

Blister Carton Label



Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name is correctly described. The established name is isavuconazonium sulfate. **Satisfactory**
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength is correctly described as186 mg isavuconazonium sulfate equivalent to 100 mg isavuconazole. **Satisfactory**
Net contents (21 CFR 201.51(a))	The net content of 14 capsules (2 blister cards) is described. **Satisfactory**
"Rx only" displayed prominently on the main panel	The statement of "Rx only" is prominently displayed. **Satisfactory**
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number (NDC 0469-0320-14) is indicated. **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	There is a space allocated for this information. **Satisfactory**
Storage conditions	Storage condition is described as: Store in original package to protect from moisture. Do not remove CRESEMBA from original packaging until your scheduled dose. Store at 20° to 25°C (68° to 77°F). **Satisfactory**
Bar code (21CFR 201.25)	Barcode is indicated. **Satisfactory**
Name of manufacturer/distributor	The name of distributor is correctly described per 21CFR 201.1. **Satisfactory**
And others, if space is available	N/A

The blister carton container label is satisfactory.

Label of the Carton Containing 4 Packs of Blisters

(b) (4)

Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name is correctly described. The established name is isavuconazonium sulfate. **Satisfactory**
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength is correctly described as186 mg isavuconazonium sulfate equivalent to 100 mg isavuconazole. **Satisfactory**
Net contents (21 CFR 201.51(a))	The net content of 4 cartons of 14 capsules is described. **Satisfactory**
"Rx only" displayed prominently on the main panel	The statement of "Rx only" is prominently displayed. **Satisfactory**
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number (NDC 0469-0320-14) is indicated. **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	There is a space allocated for this information. **Satisfactory**
Storage conditions	Storage condition is described as: Store in original package to protect from moisture. Do not remove CRESEMBA from original packaging until your scheduled dose. Store at 20° to 25°C (68° to 77°F). **Satisfactory**
Bar code (21CFR 201.25)	Barcode is indicated. **Satisfactory**
Name of manufacturer/distributor	The name of distributor is correctly described per 21CFR 201.1. **Satisfactory**
And others, if space is available	N/A

The blister carton container label is satisfactory.

Attachment - 2 (Establishment Evaluation)

(b) (4)

Yichun Sun -S

Digitally signed by Yichun Sun -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yichun Sun -S, 0.9.2342.19200300.100.1.1=1300393310
Date: 2015.03.04 14:29:36 -05'00'

Moojhong Rhee -S

Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Moojhong Rhee -S, 0.9.2342.19200300.100.1.1=1300041261
Date: 2015.03.04 14:12:24 -05'00'

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 4, 2015
FROM: Nina Ni, Ph. D., Review Chemist, Branch II, DNDP I/ONDP
THROUGH: Moo-Jhong Rhee, Ph. D., Branch Chief, Branch V, DNDP II/ONDP
TO: NDA 207501
SUBJECT: Addendum to CMC Review #1 for NDA 207501

Nina Ni -S
Digitally signed by Nina Ni -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nina Ni -S, 0.9.2342.19200300.100.1.1=2000372205
Date: 2015.03.04 14:03:38 -05'00'

Moojhong Rhee -S
Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Moojhong Rhee -S, 0.9.2342.19200300.100.1.1=1300041261
Date: 2015.03.04 14:07:54 -05'00'

In my CMC Review #1, dated 12/12/2014, this NDA was recommended for not approval due to the following issues:

1. The Office of Compliance has not made an overall "Acceptable" recommendation for the manufacturing facilities involved in this NDA.
2. Label/labeling issues were not satisfactorily resolved yet.

As of the date of this memorandum, the Office of Compliance has issued an overall "Acceptable" recommendation (date: 03/03/2015), (see the **Attachment 1)**.

The following deficiency pertinent to the labels/labeling,

- *Revise the drug product name as follows to be in line with FDA CDER naming policy as expressed in MAPP 5021.1 "Naming of Drug Products Containing Salt Drug Substances":*

(b) (4)

has been resolved as follows after an agreement was made on a t-con on February 19, 2015:

*CRESEMBA (isavuconazonium sulfate) for injection, 372 mg**

**(Equivalent to 200 mg of isavuconazole)*

(see the memorandum from Yichun Sun, Ph. D. for NDA 207500 (date: 03/04/2015) for a detailed discussion).

The updated container labels were duplicated in the **Attachment 2**.

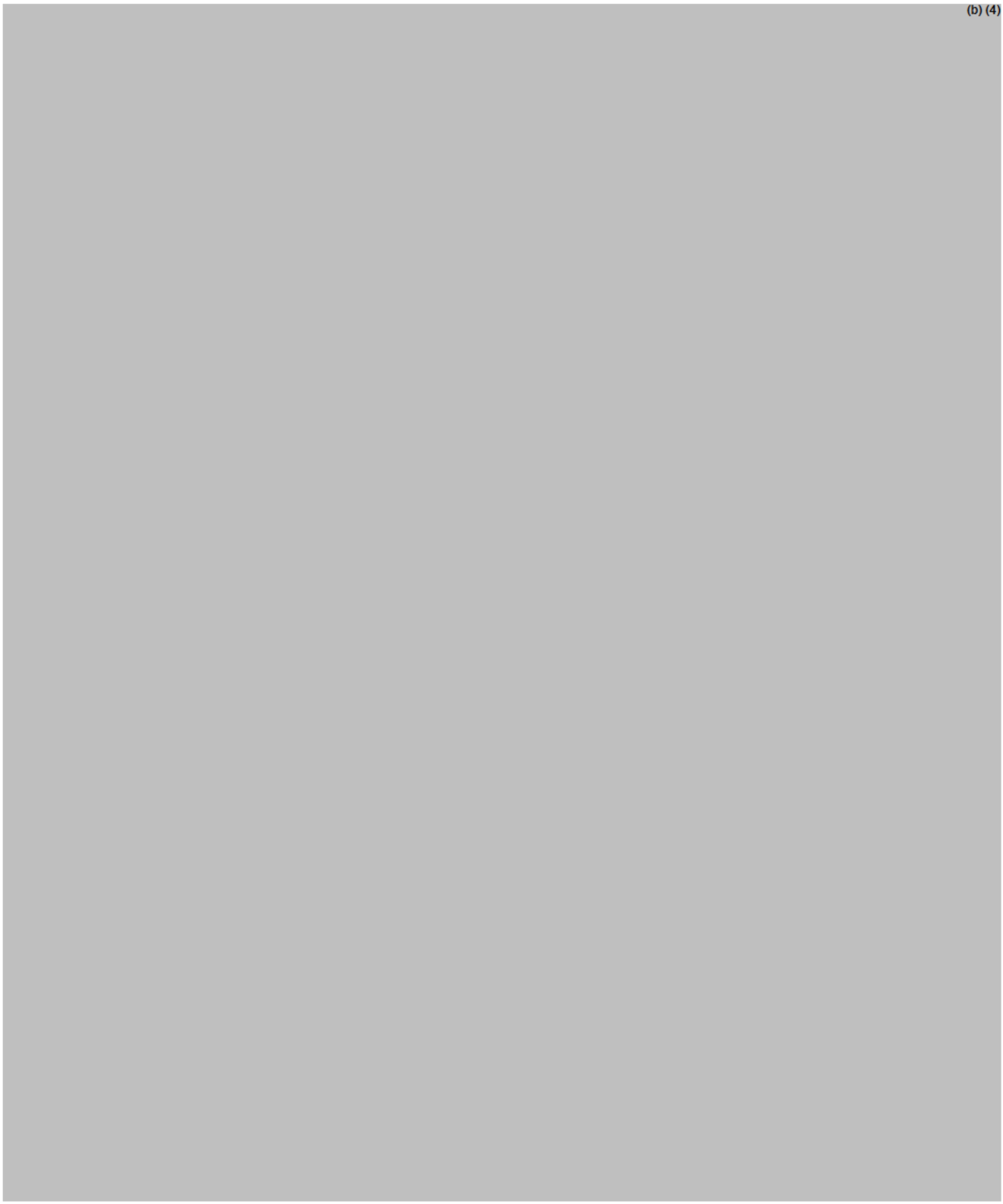
Recommendation:

As a summary, all above two issues have been satisfactorily resolved. Therefore, from the ONDP perspective, this NDA is recommended for approval with an expiration dating period of 24 months for the drug product when stored in a refrigerator.

Attachments:

Attachment 1.

Final Recommendation from Office of Compliance:

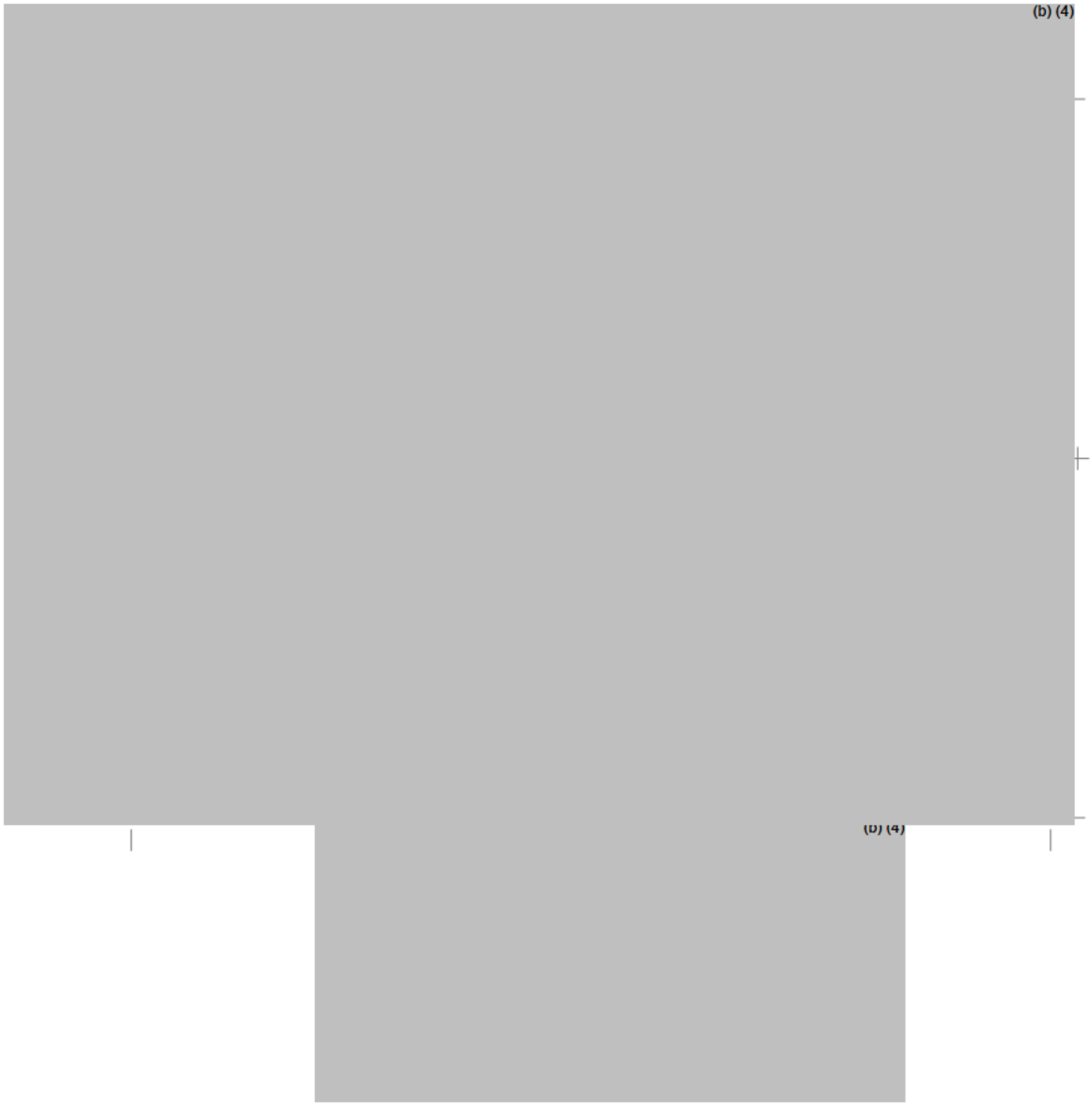


Attachment 2.

Revised Carton and Container Labels:

Carton Label:

For individual vial:



For 10 vials:

Immediate Container Vial Label:

NDA 207500

CRESEMBA® (isavuconazonium) Capsules
186.3mg

Astellas Pharma US Inc

Gene W. Holbert, Ph.D.
Yichun Sun, Ph.D.

Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

CMC REVIEW OF NDA 207500

For the Division of Anti-Infective Products (HFD-520)

Table of Contents

Chemistry Review Data Sheet

1. NDA: 207500

2. REVIEW #: 1

3. REVIEW DATE: 6-January-2015

4. REVIEWER: Gene W. Holbert, Ph.D. and Yichun Sun, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 72593	10-June-2005
Pre-NDA CMC Type B meeting	29-October-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	08-July-2014
Amendment	08-October-2014
Amendment	17-November-2014
Amendment	11-December-2014
Amendment	18-December-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Astellas Pharma US Inc.
Address:	1 Astellas way Northbrook IL 60062
Representative:	Robert M. Reed
Telephone:	224-205-8985

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Cresemba
b) Non-Proprietary Name (USAN): Isavuconazonium sulfate

c) Code Name/# (ONDQA only): BAL8557-002
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: Priority Review

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

10. PHARMACOL. CATEGORY: Triazole antifungal agent inhibiting sterol 14-alpha-demethylase, a microsomal P450 enzyme essential for ergosterol biosynthesis in fungi

11. DOSAGE FORM: Capsules (HPMC hard capsules)

12. STRENGTH/POTENCY: 100 mg isavuconazole as 186.3 mg of isavuconazonium sulfate in each capsule

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx ___OTC

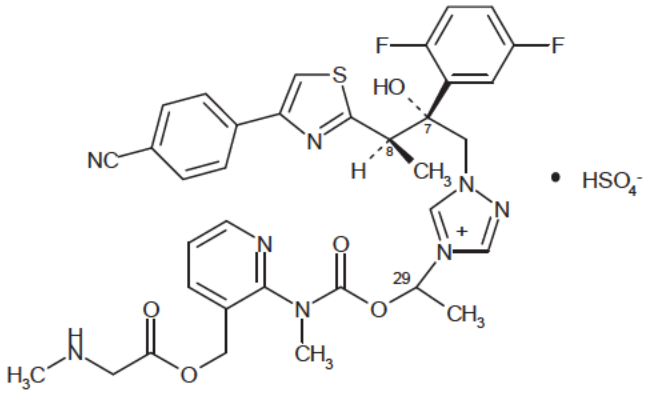
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

Glycine, N-methyl-, [2-[[[1-[1-[(2R,3R)-3-[4-(4-cyanophenyl)-2-thiazolyl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4H-1,2,4-triazolium-4-yl]ethoxy]carbonyl]methylamino]-3-pyridinyl]methyl ester, sulfate (1:1)



Structural Formula of Isavuconazonium Sulfate

Empirical formula: $C_{35}H_{35}F_2N_8O_5S \bullet H_2SO_4$

Molecular weight: 814.84

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	Adequate	NA	NA
	III			4	Adequate	NA	NA
	III			4	Adequate	NA	NA
	IV			4	Adequate	NA	NA

[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: NA

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	Pending		
Pharm/Tox	Acceptable	30-December-2014 (email)	O. G. McMaster
Biopharm	Acceptable	12-December-2014	B. S. Banu
LNC	N/A	----	----
Methods Validation	Pending		
DMEPA	N/A	----	----
EA	Claim for Categorical Exclusion is granted. See p.144	06-January-2015	Y. Sun
Microbiology	Acceptable	8-August-2014	V. B. Pawar

The Chemistry Review for NDA 207500

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, purity, strength and quality of the drug product.

However, the Office of compliance has ***not*** made a final "Acceptable" recommendation on the facilities involved.

Also, issues on labels/labeling are ***not*** completely resolved at this time.

Therefore, from the ONDQA perspective, this NDA is ***not*** ready for approval in its present form per 21 CFR 314.125(b)(6), and (13) until these issues are satisfactorily resolved.

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)

Drug Substance

Isavuconazonium sulfate (BAL8557-002) is a water-soluble triazole prodrug antifungal agent, which is hydrolyzed to the active moiety isavuconazole (isavuconazonium BAL4815) and the inactive cleavage product (BAL8728).

Isavuconazonium sulfate drug substance is an amorphous, white to yellowish white powder. The chemical name of Isavuconazonium sulfate is glycine, N-methyl-, [2-[[[1-[1-[(2R,3R)-3-[4-(4-cyanophenyl)-2-thiazolyl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4H-1,2,4-triazolium-4-yl]ethoxy]carbonyl]methylamino]-3-pyridinyl]methyl ester, sulfate (1:1). The chemical formula is $C_{35}H_{35}F_2N_8O_5S{\bullet}HSO_4$ and the molecular weight is 814.84. Isavuconazole, the active moiety, has a molecular formula of $C_{22}H_{17}F_2N_5OS$ and a molecular weight of 437.47. Isavuconazonium sulfate sparingly soluble in ethanol but very soluble in wate[redacted] (b) (4) [redacted] (b) (4) [redacted] The proposed acceptance criteria for the potential genotoxic impurities are deemed acceptable (see **Attachment 2**).

Drug Product

The drug product, CRESEMBA (isavuconazonium sulfate) capsules, is indicated for use in the treatment of invasive aspergillosis and invasive mucormycosis. The active ingredient,

Isavuconazonium sulfate, is a prodrug containing isavuconazole, a triazole antifungal agent. The capsules have a Swedish Orange (reddish-brown color) body and a white cap. The capsules are imprinted with "ISA" (cap) and the Astellas logo (body) in black ink. Each CRESEMBA capsule contains 186.3 mg isavuconazonium sulfate, corresponding to 100 mg isavuconazole. The inactive ingredients include magnesium citrate, microcrystalline cellulose, talc, colloidal silicon dioxide, and stearic acid. The isavuconazonium capsules are packaged in in aluminum / aluminum blisters with desiccant. The isavuconazonium capsules are prepared by (b) (4) The manufacturing process of the drug product includes the following steps: (b) (4)
The in-process controls implemented during the drug product manufacturing process are (b) (4) The identity, strength, purity and quality of the drug product are adequately controlled by the drug product specification. The acceptance criterion of the dissolution test has been finalized and accepted (see Biopharm Review dated 12-12-14). The proposed expiration dating period of 30 months is supported by the primary and supportive long-term and accelerated stability data provided. The drug product qualifies for categorical exclusion from the preparation of an environmental assessment according to 21 CFR 25.31(b).

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

CRESEMBA is a prodrug containing isavuconazole, a triazole antifungal agent, indicated for use in the treatment of invasive aspergillosis and invasive mucormycosis. The loading dose is 200 mg every 8 hours, for 48 hours (6 total doses), via oral or IV administration. The maintenance dose is 200 mg once per day via oral or IV administration starting 12 to 24 hours after the last loading dose. Switching between the IV and oral formulations of CRESEMBA is acceptable as bioequivalence (mg:mg) has been demonstrated. Loading dose is not required when switching between formulations. Intravenous formulation is not for bolus injection, administer intravenous dose via an infusion set with an in-line filter (pore size 0.2 µm to 1.2 µm) over a minimum of 1 hour. With oral administration, capsules should be swallowed whole. Do not chew, crush, dissolve, or open the capsules. CRESEMBA can be taken with or without food.

C. Basis for Not-Approval Recommendation

21CFR 314.125(b)(6)

- Label and labeling issues have not been resolved (see list of deficiencies)

21CFR 314.125(b)(13)

- The Office of Compliance has not made a final "Acceptable" recommendation on the facilities involved.

(see the **List of Deficiencies** on p.226)

III. Life Cycle Knowledge Management

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation approach in control strategy**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay	• Formulation • Raw materials • Process parameters • scale/equipment • Site	L	(b) (4) The drug product is packaged in aluminum/ aluminum blisters with desiccant.	Acceptable	In-process controls are detailed in the master batch record.
Physical stability (solid state)	The API is a (b) (4) amorphous powder.	L	Very soluble in water	Acceptable	
Content Uniformity	(b) (4) processes	L	(b) (4)	Acceptable	
Microbial Limits	Raw materials; Manufacturing process	L	API and excipients meet the microbial specifications. (b) (4)	Acceptable	

			(b) (4)		
Impurities/related substances/residual solvents	Quality of API (large number of impurities); Manufacturing processes; Raw materials; Analytical procedures;	L	Residual solvent and related substances are controlled according to the drug substance specification. (b) (4)	Acceptable	
Dissolution	Formulation; Raw materials (disintegration of capsule shell); Attributes of API (e.g. particle size)	L	(b) (4)	Acceptable	

			(b) (4)		

IV. Administrative

A. Reviewer's Signature

G. W. Holbert, Ph.D.
Reviewer

Gene W. Holbert -A
Digitally signed by Gene W Holbert -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13001 2836, cn=Gene W Holbert -A
Date: 2015.01.06 11:13:54 -05'00'

Date

Yichun Sun, Ph.D.
Reviewer

Yichun Sun -A
Digitally signed by Yichun Sun -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yichun Sun -A, 0.9.2342.19200300.100.1.1=1300393310
Date: 2015.01.06 09:58:37 -05'00'

Date

B. Endorsement Block

Moo-Jhong Rhee, Ph.D.
Branch Chief

Date

Moojhong Rhee -S
Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Moojhong Rhee -S, 0.9.2342.19200300.100.1.1=1300041261
Date: 2015.01.06 17:54:23 -05'00'

C. CC Block

Dorota Matecka, Ph.D.
CMC lead

Date

Navi Bhandari, M.S.
Project Manager

Date

215 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

IV. Attachments

Attachment 1:

Establishment Evaluation Summary

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 207500/000	**Sponsor:**	ASTELLAS
Org. Code:	520		1 ASTELLAS WAY
Priority:	1		NORTHBROOK, IL 60062
Stamp Date:	08-JUL-2014	**Brand Name:**	ISAVUCONAZONIUM SULFATE (BAL8557)
PDUFA Date:	08-MAR-2015	**Estab. Name:**	
Action Goal:		**Generic Name:**	ISAVUCONAZONIUM SULFATE (BAL8557)
District Goal:	08-NOV-2014	**Product Number; Dosage Form; Ingredient; Strengths**	001; CAPSULE; ISAVUCONAZONIUM SULFATE; 100MG

FDA Contacts:	Y. SUN	Prod Qual Reviewer		3017961388
	V. PAWAR	Micro Reviewer	(HFD-805)	3017961587
	N. BHANDARI	Product Quality PM		2404023815
	A. RODGERS	Regulatory Project Mgr	(HFD-520)	3017960797

Overall Recommendation: PENDING on 07-AUG-2014 by EES_PROD

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 08-AUG-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: INSPECTION SCHEDULED

Milestone Date: 18-SEP-2014

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4) (b) (4)	
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	14-AUG-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:**	**FEI:** (b) (4) (b) (4)	
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	ASSIGNED INSPECTION TO IB		
Milestone Date:	12-AUG-2014		

Establishment:	**CFN:**	**FEI:** (b) (4) (b) (4)	
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	CAPSULES, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	INSPECTION SCHEDULED		
Milestone Date:	16-SEP-2014		

Attachment 2:

(Email from pharm/tox reviewer, Dr. Owen G. McMaster)

From:	McMaster, Owen G
Sent:	Tuesday, December 30, 2014 12:05 PM
To:	Matecka, Dorota M; Rhee, Moo Jhong; Holbert, Gene W; Ni, Nina; Sun, Yichun
Cc:	Schmidt, Wendelyn J; Rodgers, Alison
Subject:	RE: NDAs 207500 and 2075001 - impurities

Hi All:

After reviewing the corrected numbers from Astellas, I have concluded that the drug product and drug substance specifications are acceptable from Pharm/Tox perspective.

NDA 207501

Cresemba® (isavuconazonium) for Injection, (b) (4) mg/Vial
Astellas Pharma US Inc.

Nina Ni, Ph. D.

Review Chemist

Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

CMC REVIEW
For the Division of Anti-Infective Products

Table of Contents

CMC Review Data Sheet

1. NDA 207501

2. REVIEW #: 1

3. REVIEW DATE: 12/12/2014

4. REVIEWER: Nina Ni, Ph. D.

5. PREVIOUS DOCUMENTS:

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission Correspondence (C)	07/08/2014
Amendment (BC): 0006	09/04/2014
Amendment (BC): 0009	09/26/2014
Amendment (BC): 0011	11/10/2014
Amendment (BC): 0014	11/17/2014
Amendment (BC): 0018	12/11/2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Astellas Pharma US Inc.
Address:	1 Astellas Way Northbrook, IL 60062
Representative:	Robert M. Reed, Senior Director, Regulatory Affairs
Telephone:	224-205-8985

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Cresemba
b) Non-Proprietary Name (USAN): Isavuconazonium sulfate
c) Code Name/# (ONDQA only): BAL8557-02, ASP9766
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: Type I
- Submission Priority: Priority

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

10. PHARMACOL. CATEGORY: Anti-fungal agent

11. DOSAGE FORM: Powder for injection

12. STRENGTH/POTENCY: (b) (4) i.e., 372.6 mg isavuconzaonium sulfate, i.e., 200 mg isavuconazole

13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED: __√__ Rx ___ OTC

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

_____SPOTS product – Form Completed

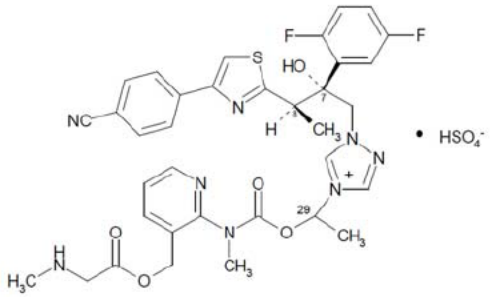
__√__ Not a SPOTS product

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

NAME: Isavuconazonium sulfate

CHEMICAL NAME (b) (4)

STRUCTURAL FORMULA:



MOLECURAL FORMULA: $C_{35}H_{35}F_2N_8O_5S \cdot HSO_4$

MOLECULAR WEIGHT: 814.84

CAS NUMBER: 946075-13-4

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	N/A		
	III			4	N/A		

[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
IND	72593	

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending		
Pharm/Tox	NA		
Biopharm	NA		
LNC			
Methods Validation	Pending		
DMEPA			
EA	Claim for the categorical exclusion is submitted to meet 21 CFR 314.50 (d)(1)(iii)		
Microbiology	Approval	11/21/2014	Vinayak Pawar, Ph. D.

The CMC Review for NDA 207501

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

However, the Office of Compliance has ***not*** made an overall "Acceptable" recommendation for the facilities involved in this NDA.

Also, issues on label/labeling have ***not*** been resolved.

Therefore, from the ONDQA perspective, this NDA is ***not*** ready for approval in its present form until all the pending issues are satisfactorily resolved.

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

NA

II. Summary of CMC Assessments

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

On July 8, 2014, the applicant concurrently submitted two original NDAs (207500 and 207501) for isavuconazonium sulfate, a water soluble triazole product with the proprietary name, Cresemba®. Cresemba® is available as a sterile lyophilized powder for intravenous infusion (NDA 207501) and as hard capsules for oral administration (NDA 207500). NDA 207501 only contains drug product information (CTD Module 3.2.P) for the intravenous formulation and incorporates all remaining CTD Modules via cross reference to NDA 207500 which contains drug substance to support both NDAs and drug product information for the hard capsules.

(1) Drug Substance

The applicant has referenced to NDA 207500 for the whole CMC section of the drug substance. Gene Holbert, Ph. D. has reviewed the drug substance section for NDA 207500 and found adequate to support both NDAs. Please see his review on the drug substance for NDA 207500 for a detailed evaluation.

(2) Drug Product

Executive Summary Section

Isavuconazonium sulfate for injection is a sterile, lyophilized product containing 372.6 mg isavuconazonium sulfate, corresponding to 200 mg isavuconazole (active moiety, BAL4815) per vial. The inactive ingredients include mannitol as a bulking agent and sulfuric acid for pH adjustment. All excipients are compendial grade. The levels of usage of each inactive ingredient in this final drug product are lower than those listed in IIG for the same route of administration.

The container closure system for the drug product consists of 10 mL vial, 20 mm stopper, and 20 mm aluminum/flip-off seal. All the components comply with the pertinent 21CFR regulations for direct food contact. The applicant has demonstrated the compatibility, suitability, functionality, and safety of the primary and in-use container closure system with the drug product.

The IV formulation of isavuconazole sulfate is to be administered by intravenous infusion after reconstitution with 5.0 mL of water for injection and further dilution with 0.9% sodium chloride (saline) solution or 5% dextrose solution (D5W). The instructions for use in the labeling state that the infusion solution should be administered through an inline filter (0.2 to 1.2 µm pore size), placed between the infusion bag and patient access. In addition, the reconstituted solution may be stored for up to one hour prior to preparation of the infusion solution. The prepared infusion solution should be kept for not more than 6 hours at room temperature or 24 hours in a refrigerated at 2° to 8°C prior to use.

A white precipitate formed during preparation of the administration solution when the reconstituted solution was mixed with saline and D5W. Although this precipitate was observed throughout the compatibility study, the assay and impurity values were consistent. The precipitate has been conclusively identified as BAL4815, the active moiety present in the lyophilized drug product and not from hydrolysis of the product in the infusion solution since the precipitates are formed right away. Thus, the applicant has proposed that the product labeling includes a statement that the infusion solution may contain visible particles and therefore a requirement for the use of an inline filter.

The manufacturing process of isavuconazonium sulfate for injection consists of the following steps: (b) (4) The proposed commercial target batch size is (b) (4) and it can vary based on the (b) (4). The manufacturing process appears to be straightforward and well defined in terms of (b) (4) The proposed in-process controls are deemed adequate to assure the completion of (b) (4)

The proposed drug product specification which includes description, identification, pH, related substances, BAL4815, 2-butenal, water content, bacterial endotoxins, uniformity of dosage units, foreign matter, particulate matter, sterility, and assay is supported by data and acceptable.

The to-be-marketed formulation is the same formulation used in Phase 3 clinical trials. The drug product stability submitted in the NDA includes up to 18 months stability data for three registration batches. All three batches were manufactured at the intended commercial manufacturing site, (b) (4) with the intended commercial manufacturing process on the commercial scale, and packaged in the commercial packaging components of type I glass vial with rubber stopper.

The stability data indicate that the drug product is physically and chemically stable with no significant change when stored in a refrigerator for up to 18 months. All tested attributes are within the specification. The stability data support the proposed shelf life of 24 months for isavuconazonium IV drug product when stored in a refrigerator.

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

The IV formulation of isavuconazole sulfate is to be administered by intravenous infusion after reconstitution with 5.0 mL of water for injection and further dilution with 0.9% sodium chloride solution or 5% dextrose solution. The reconstituted solution may be stored for up to one hour prior to preparation of the infusion solution. The prepared infusion solution should be kept for not more than 6 hours at room temperature [20°C to 25°C (68°F to 77°F)] or 24 hours at 2° to 8°C (36° to 46°F) prior to use. The prepared infusion solution must be administered through an in-line filter over a minimum of 1 hour. CRESEMBA for injection vials are for single use only and any unused reconstituted solution should be discarded.

C. Basis for Not-Approval Recommendation

21 CFR 314.125 (b)(13)

- The Office of Compliance has **not** made an overall "Acceptable" recommendation for the manufacturing facilities.

21 CFR 314.125 (b)(6)

- Issues on labels and labeling have **not** been resolved yet.

(see the **List of the Deficiencies** on p. 96).

III. Lifecycle Knowledge Management

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation approach in control strategy**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay for	Quality of the	L		Acceptable	

Isavuconazonium Sulfate	incoming API; DP storage; Analytical procedure				
Physical stability (solid state)	Stability; (b) (4) Manufacturing process	L	(b) (4)	Acceptable	
Uniformity of Dosage Units	Assay analytical procedure; Manufacturing process	L	(b) (4)	Acceptable	
Particulate matter	Manufacturing process; diluent	H	In-line filter is proposed in labeling	Acceptable	
Impurities/degradation products including extractables and leachables	(b) (4) impurities (b) (4)	H	(b) (4)	Acceptable	
BET/Sterility	Manufacturing processes, (b) (4)	H	Adequate controls in place	Acceptable	

*Risk ranking applies to product attribute/CQA

**For example, post marketing commitment, knowledge management post approval, etc.

IV. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Nina Ni, Ph. D., CMC Reviewer, Branch IV, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph. D., Branch Chief, Branch IV, ONDQA

C. CC Block: entered electronically in DFS

Dorota Matecka, Ph.D., CMC Lead, Branch V, ONDQA

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IV. Attachment

EES Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 207501/000	**Action Goal:**	
Stamp Date:	08-JUL-2014	**District Goal:**	08-NOV-2014
Regulatory:	08-MAR-2015		
Applicant:	ASTELLAS	**Brand Name:**	ISAVUCONAZONIUM SULFATE (BAL8557)
	1 ASTELLAS WAY	**Estab. Name:**	
	NORTHBROOK, IL 60062	**Generic Name:**	ISAVUCONAZONIUM SULFATE (BAL8557)
Priority:	1	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	520	001; POWDER; ISAVUCONAZONIUM SULFATE; 200MG	

Application Comment:

FDA Contacts:	N. NI	Prod Qual Reviewer		3017965296
	V. PAWAR	Micro Reviewer	(HFD-805)	3017961587
	N. BHANDARI	Product Quality PM		2404023815
	A. RODGERS	Regulatory Project Mgr	(HFD-520)	3017960797

Overall Recommendation: PENDING on 07-AUG-2014 by EES_PROD

CMC Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities:
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STERILITY TESTER

Establishment Comment: (b) (4)

Profile: (b) (4), LYOPHILIZED **OAI Status:** NONE

Milestone Name / Comment / OAI Submit To OC / Request to Extend Re-eval Date To / Extension Request Comment / Reason	Milestone Date	Request Type	Planned Completion	Decision	Creator
SUBMITTED TO OC	07-AUG-2014				BHANDARIN
SUBMITTED TO DO NME	08-AUG-2014	Product Specific and GMP Inspection			RHX
ASSIGNED INSPECTION TO IB NME	19-AUG-2014	Product Specific and GMP Inspection			DOMBROWSKIR

CMC Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: (b) (4)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Milestone Name / Comment / OAI Submit To OC / Request to Extend Re-eval Date To / Extension Request Comment / Reason	Milestone Date	Request Type	Planned Completion	Decision	Creator
SUBMITTED TO OC	07-AUG-2014				BHANDARIN
SUBMITTED TO DO NME	08-AUG-2014	Product Specific and GMP Inspection			RHX
ASSIGNED INSPECTION TO IB	13-AUG-2014	Product Specific and GMP Inspection			MROSE
INSPECTION SCHEDULED	(b) (4)				EBUTLER

CMC Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: (b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	07-AUG-2014				BHANDARIN
SUBMITTED TO DO	08-AUG-2014	Product Specific and GMP Inspection			RHX
NME					
DO RECOMMENDATION	13-AUG-2014			ACCEPTABLE	MROSE
OC RECOMMENDATION	14-AUG-2014			ACCEPTABLE	WILLIAMSJU

CMC Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: (b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name / Comment / OAI Submit To OC / Request to Extend Re-eval Date To / Extension Request Comment / Reason	Milestone Date	Request Type	Planned Completion	Decision	Creator
SUBMITTED TO OC	07-AUG-2014				BHANDARIN
SUBMITTED TO DO	08-AUG-2014	Product Specific and GMP Inspection			RHX
NME					
UNDER REVIEW	16-AUG-2014				MROSE

Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **207500**

2. DATES AND GOALS:

Letter Date: July 8, 2014	Submission Received Date: July 8, 2014
PDUFA Goal Date: March 8, 2015	

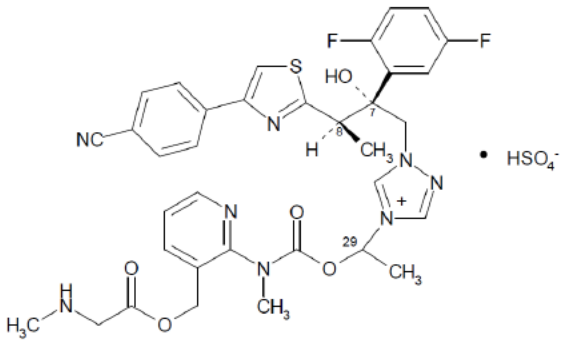
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	CRESEMBA® (*proposed*)
Established or Non-Proprietary Name (USAN):	Isavuconazonium sulfate
Dosage Form:	Capsules
Route of Administration	Oral
Strength/Potency	186.3 mg of isavuconazonium sulfate (equivalent to 100 mg isavuconazole)
Rx/OTC Dispensed:	Rx

4. INDICATION:

Treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older.

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



Molecular Formula: $C_{35}H_{35}F_2N_8O_5S \cdot HSO_4$

Molecular Weight: 814.84†

Molecular Weight of Active Moiety (isavuconazole): 437.47†

6. NAME OF APPLICANT (as indicated on Form 356h):

   Astellas Pharma US Inc.

7. SUBMISSION PROPERTIES:

Review Priority:	Priority (PDUFA V)
Submission Classification (Chemical Classification Code):	1
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DAIP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology			*TBD*
Establishment Evaluation Request (EER)		X	Submitted August 7, 2014
Pharmacology/Toxicology	X		
Methods Validation	X		Submitted on August 18, 2014
Environmental Assessment		X	Categorical exclusion claim
CDRH			N/A
Other			N/A

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? **Yes**
CMC Filing Issues:
N/A

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? **No**
CMC Comments for 74-Day Letter:
N/A

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? **Yes**
Biopharmaceutics Filing Issues:
N/A

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? **Yes**
Biopharmaceutics Comments for 74-Day Letter:
1. *We could not locate in your NDA submission the complete dissolution profile data for the clinical and registration batches of your drug product. Please provide the data collected at 15, 20, 30, 45, 60, 75 and 90 minutes for the clinical and registration batches (i.e., individual, mean, SD, profiles; n=12); or if submitted, indicate where these data are located.* 2. *To support the bridging between the clinical and commercial drug products, provide the dissolution profile comparison data (n=12) with the statistical testing comparing the profiles for the clinical and commercial batches using the proposed dissolution method.* *Please note, that if the percent coefficient of variation is higher than 20% for earlier time points (i.e., 10, 15 min) or higher than 10% for the other time points the f2 test cannot be used and therefore alternative methods (i.e., multivariate model independent or dependent approaches) should be used to estimate the profiles similarity. For detail information on the requirements/ limitations of f2 testing, please refer to the dissolution guidance (FDA CDER Guidance for Industry-Dissolution Testing of Immediate Release Solid Oral Dosage Forms" August 1997). If an alternative method is used, include all the input and output files generated for this analysis.*

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? **Yes**
Microbiology Filing Issues:
See Microbiology Filing Review for details and for any potential Microbiology review issues.

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
	X		

Is a team review recommended?	Yes X	No
Suggested expertise for team:		
Quality (CMC, Microbiology and Biopharmaceutics) Review Team: *Gene Holbert, Ph.D. (drug substance reviewer)* *Yichun Sun, Ph.D. (drug product reviewer)* *Vinnie Pawar, Ph.D. (product quality microbiology reviewer)* *Banu Zolnik, Ph.D. (biopharmaceutics reviewer)*		

Summary of Critical Issues and Complexities:

This NDA provides for an oral dosage form (capsules) of a new synthetic antifungal drug, isavuconazonium sulfate. CMC information for both, the drug substance and the drug product, has been provided in the NDA. As this NDA presents a new molecular entity, critical issues will most likely include assessment of the proposed synthesis, structure elucidation, stability and purity of the proposed drug substance. The NDA section 3.2.S.3.2 includes an extensive discussion of the drug substance impurities, their origin, fate, qualified levels, genotoxic assessment, and controls. It should be noted that this applicant has submitted a concurrent NDA for an IV formulation of isavuconazonium sulfate (NDA 207501). CMC information for the drug substance is provided in the current NDA (207500).

For a brief summary of the proposed drug product, isavuconazonium sulfate capsules, refer to the IQA below.

Initial Quality Assessment

Isavuconazonium sulfate (BAL8557-002, also referred to as ASP9766) is a water-soluble triazole prodrug. The prodrug is hydrolyzed *in vivo* by plasma esterases to form BAL4815 (isavuconazole, the active moiety), and BAL8728 (an inactive cleavage product). Isavuconazole acts by inhibiting sterol 14-alpha-demethylase, a microsomal P450 enzyme essential for ergosterol biosynthesis in fungi. Isavuconazole demonstrates good in vitro activity against *Aspergillus* spp., Mucormycetes, *Candida* spp. and numerous other filamentous fungi, yeasts and dimorphic fungi. Isavuconazonium is indicated for the treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older.

Isavuconazonium compound was specifically developed to facilitate intravenous administration, without the need for nephrotoxic excipients such as cyclodextrin. Isavuconazonium is available for administration parenterally via intravenous infusion as powder for concentrate for solution for infusion and orally as hard capsules. The proposed therapeutic dose of isavuconazonium is expressed in terms of the quantity of the active moiety: isavuconazole. For intravenous infusion, the dosage strength of the sterile lyophilized powder of 372.6 mg isavuconazonium sulfate corresponds to 200 mg isavuconazole per vial. For oral delivery, the dosage strength of the hard capsule formulation of 186.3 mg isavuconazonium sulfate corresponds to 100 mg of isavuconazole. The oral formulation, which is almost completely bioavailable, can be used in place of the intravenous formulation at any time.

Isavuconazole is administered using a loading dose followed by maintenance dosing:

- Loading dose: 200 mg every 8 hours for the first 48 hours via oral or intravenous administration
- Maintenance dose: 200 mg per day via oral or intravenous administration

The intravenous formulation of isavuconazonium sulfate (sterile lyophilized powder for injection) was developed through IND 72593 and the oral formulation (capsules) was developed via IND 119307. In the course of development, isavuconazonium sulfate was granted a Qualified Infectious Disease Product (QIDP) and Orphan Drug designations.

Several meetings were held during the drug development between the applicant and the FDA. The correspondences relevant to CMC activities during the development of these products (as documented in DARRTS) include:

1. Type C meeting on June 6, 2014 (preliminary responses sent June 3, 2014; meeting cancelled by the Sponsor)

2. Pre-NDA meeting on October 29, 2013 (preliminary responses dated October 25, 2013 and meeting minutes dated November 29, 2013)

3. Type C CMC Guidance meeting on January 17, 2012 (preliminary responses dated January 11, 2012 and meeting minutes dated September 26, 2013)

Drug Substance

The isavuconazonium sulfate drug substance, a pro-drug of the active triazole isavuconazole (BAL4815), is regarded as highly soluble. Isavuconazonium sulfate drug substance is an amorphous and hygroscopic material. Isavuconazonium sulfate has three chiral centers at C7 (*R*), C8 (*R*), and C29 (*R/S*). Drug substance is a (b) (4). (b) (4) Data on characterization of the structure and potential impurities has been provided. In addition, information on impurities includes a discussion of potentially genotoxic impurities. *Comments: Information provided in the NDA including the proposed limits for impurities (quite a large number) and toxicological justification in both drug substance and the drug product should be discussed with the pharm/tox reviewer of this application. It should be noted that the impurity profile and issues around the potentially genotoxic impurities were discussed with the applicant previously at the above mentioned meetings with the participation of the pharm/tox team.*

The synthesis of isavuconazonium sulfate involves (b) (4) (a flow chart is reproduced in Attachment I, below). There are (b) (4) in the manufacture of drug substance: (b) (4) *Comment: It should be noted that the designation of the regulatory starting materials was discussed with the applicant at the January 17, 2012 meeting.* The same synthetic route has been used throughout clinical development with minor modifications, which have been discussed in Section 3.2.S.2.6. For nonclinical, Phase I and Phase II study supplies, the drug substance was (b) (4)

The proposed drug substance specification is attached below (Attachment II). It includes accep ce criteria for a number of impurities with the total impurities acceptance criterion of NMT (b) (4) %.

Stability data include results for three primary stability batches manufactured at the proposed commercial site. The sizes of these batches are approximately (b) (4) kg to (b) (4) kg; the projected commercial size is up to (b) (4) kg. These data include 24 months of stability results for the drug substance stored at -20 ± 5°C for the three primary batches and 12 months of results at 5 ± 3°C for seven batches (including primary stability batches). In addition, the results of stress and force-degradation studies have also been provided. A (b) (4) month retest period is proposed for isavuconazonium sulfate drug substance packaged in (b) (4)

[redacted], and stored at [redacted] *Comment: The proposed retest date will need to be evaluated based on the overall data submitted in the NDA.*

Drug Product

Isavuconazonium sulfate capsules are hard capsules containing 186.3 mg isavuconazonium sulfate corresponding to 100 mg isavuconazole (active moiety BAL4815). The capsules have a Swedish Orange (reddish-brown color) body and a white cap. The capsules are imprinted with "ISA" (cap) and the Astellas logo (body) in black ink. Isavuconazonium sulfate capsules are packaged in aluminum/aluminum blisters with desiccant.

Composition of the proposed capsules that includes the compendial status of the excipients is reproduced below (Attachment III). No novel excipients are used for isavuconazonium capsules. The applicant stated that none of excipients used in the manufacturing of isavuconazonium capsules is of human or animal origin. Hard hypromellose capsule [redacted] Capsules) is used as the capsule shell. The capsule shell composition is described in the NDA; in addition, a reference is made to DMF Type IV [redacted] held by [redacted] *Comment: The applicant stated that the proposed commercial formulation is the same as the formulation that has been used in Phase III clinical studies except the capsule shells used in Phase III clinical studies are different in color and imprint from the commercial capsules. The applicant also stated that the proposed commercial-scale manufacturing processes will be the same as those for the production of Phase III clinical trial material batches.*

Isavuconazonium capsules are manufactured using conventional and well-established pharmaceutical production equipment and conventional unit operations. Isavuconazonium sulfate is [redacted] (refer to the manufacturing process flow diagram for isavuconazonium capsules attached below – Attachment IV). The commercial batch size is stated to be [redacted] capsules.

The proposed drug product specification (attached below; Attachment V) includes the following tests: description, assay, related substances, dissolution, [redacted], microbial limits, identification, and uniformity of dosage units. *Comment: It should be noted that the Product Quality Microbiology review recommending approval has been filed in DARRTS (by Dr. Vinnie Pawar).*

The isavuconazonium sulfate capsules will be packaged in blisters (as aluminum blister pack with seven capsules per sheet and desiccant). Stability information submitted in the NDA for the proposed drug product includes stability data for three registration batches [redacted] capsules each):

Table 21 Batch Information

Batch No	2048-11501A	2048-11502A	2048-11503A
Manufacturing/Packaging site	(b) (4)		
Manufacturing date	Dec 2011		
Batch size (capsules)	(b) (4)		
Drug substance batch	17CH03SD.HQ00022	17CH03SD.HQ00023 + 17CH03SD.HQ00024	17CH03SD.HQ00024
Packaging configuration	Al-Al blister with desiccant		
Test facilities	(b) (4)		

Based on the 18 months of stability data for the three registration batches and the statistical analyses, the applicant is proposing an initial shelf life of 30 months for isavuconazonium capsules when stored in aluminum/aluminum blister with desiccant at controlled room temperature. *Comment: The proposed shelf life will be assessed based on the overall data submitted.*

Risk Assessment

Product attribute/ CQA	Factors that can impact the CQA	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	FMEC A RPN Number	Comment, if any
Assay for Isavuconazonium Sulfate	Quality of the incoming API; Analytical procedure	2	3	1	6	Evaluate the in-coming material specification and COA provided; evaluate the assay method
Physical stability (solid state)	Stability; (b) (4) Manufacturing process	3	3	4	36	Any potential for solid state changes?
Content uniformity	Assay analytical procedure; Manufacturing process	2	3	3	18	Evaluate analytical procedures; in-process controls
Microbial Limits	Raw materials; Container closure	1	2	5	10	Consult Product Quality Microbiology

						Review
Impurities including residual solvents	Quality of API (large number of impurities); Manufacturing processes; Raw materials; Analytical procedures;	4	4	4	64	Evaluate control strategy for genotoxic impurities and other impurities; see CoAs for excipients; any testing per <467>? Consult with the Pharm/Tox Reviewer
Dissolution	Formulation; Raw materials (disintegration of capsule shell); Attributes of API (e.g. particle size)	4	3	4	48	Consult Biopharmaceutics Reviewer

RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)

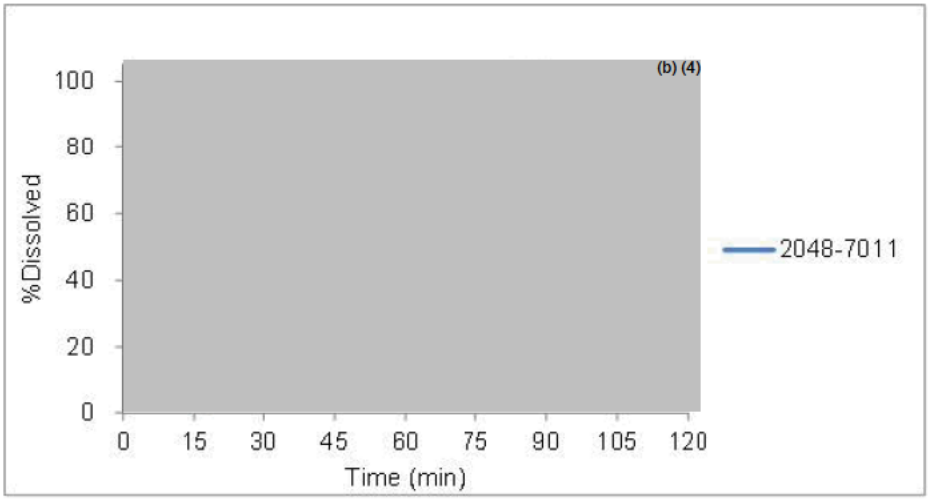
Initial Quality-Biopharmaceutics Assessment

Biopharmaceutics Synopsis, Critical Issues or Complexities
Submission: This 505 (b)(1) NDA submission contains isavuconazonium sulfate in a hard capsule oral formulation.
Introduction: Isavuconazonium sulfate is a water-soluble triazole prodrug. Isavuconazole acts by inhibiting sterol 14-alpha-demyhlase, a microsomal p450 enzyme essential for ergosterol biosynthesis in fungi. Isavuconazonium is indicated for the treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older.
Drug Product Description: Isavuconazonium sulfate is an amorphous material and solubility of the drug substance is reported to be (b) (4) The Applicant states that isavuconazonium is (b) (4) The Applicant is reporting isavuconazonium sulfate as a BCS Class 1 (high solubility and high permeability) drug substance; however, it is noted that its (b) (4) The Applicant submitted bioavailability study No. 9766-CL-0010 following single oral and intravenous administration of isavuconazonium sulfate. This study will be reviewed by the Office of Clinical Pharmacology. The Applicant reported that the mean absolute bioavailability of isavuconazole as 98% following a single dose oral administration and therefore, they consider that the oral formulation under NDA 207500 can be used in place of the intravenous formulation under NDA 207501 at any time. The formulation of the proposed commercial drug product is the same as the formulation of the drug product that was used in Phase 3 clinical studies, except for the capsule's shells, which are different in color and imprint from those used for the commercial capsules. Therefore, the dissolution profiles of the clinical and commercial drug products should be compared to determine the impact of color change on the drug release. Since this information was not provided in the NDA, a comment requesting this information will be conveyed to the Applicant in the 74-Day letter. It is noted that isavuconazonium chloride was used for the clinical Phase 1 and Phase 2 studies, instead of isavuconazonium sulfate. The Applicant is proposing to use the following dissolution method and acceptance criterion for

the proposed drug product:

USP Apparatus/RPM	Medium	Volume	Acceptance Criterion
USP II (paddle with sinker) at 75 rpm	Diluted McIlvaine Buffer pH 6 + 0.5 % SLS,	900 mL	Q= (b) (4)% in 75 minutes

Figure 1 Dissolution Behavior of 13 Clinical Batches and 3 Registration Batches of Isavuconazonium Capsules. (Apparatus 2, 75 rpm, Diluted McIlvaine Buffer pH6 with 0.5% SLS)



The blue line represents the dissolution profile of the batch 2048-7011, which is a biobatch used in the absolute bioavailability study (9766-CL-0010). The black lines represent the dissolution profiles of the other 12 clinical batches and 3 registration batches.

**Batch 204807011 is the bio-batch used in the absolute bioavailability study of isavuconazole after oral and IV administration.*

The Applicant states that the rate limiting step for the dissolution of this drug product is the shell capsule ((b) (4), hypromellose (HPMC) capsule containing gellan gum), (b) (4)

The following information was submitted to support the selection of the proposed dissolution method:

1) Effect of agitation speed
2) Effect of surfactant (0%, 0.1%, 0.25%, 0.5%, 1%).
3) Discriminating ability of the dissolution method is tested by evaluating different brand of HPMC capsules with similar composition

Review Objectives:
The Biopharmaceutics review will be focused on the evaluation of the proposed dissolution method and acceptance criteria and the dissolution information supporting the bridging between the clinical and commercial drug products.

Issues Identified:
The complete dissolution profile data for the bio- and registration batches were not provided in the NDA submission. Also, the dissolution profile comparison data bridging the clinical and commercial drug products were not included. Therefore, Biopharmaceutics comments requesting this information will be included in the 74-Day letter (refer to page 3 of this document).

Filing Recommendation:
The NDA is fileable from a Biopharmaceutics perspective. However, some dissolution data are lacking and Biopharmaceutics has comments which will be conveyed to the Applicant in the 74-Day letter or in an earlier IR communication.

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			*N/A*

	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		*Categorical exclusion claim*

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			*Some QbD elements (CQAs, DoEs, risk assessment, control strategy)*
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			*Not immediately obvious (but not required either)*

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		Section 3.2.R
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
24.	Does the section contain controls of the final drug product?	X		
25.	Has stability data and analysis been provided to support the requested expiration date?	X		18 months for three primary stability batches
26.	Does the application contain Quality by Design (QbD) information regarding the DP?			*QbD elements (CQAs, DoEs, risk assessment, control strategy)*
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			*Not immediately obvious (but not required either)*

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
28.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			*N/A*

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III		(b) (4)	5/25/2014	
	III			5/24/2014	
	III			5/23/2014	
	III			2/25/2014	

I. LABELING				
	Parameter	Yes	No	Comment
31.	Has the draft package insert been provided?	X		
32.	Have the immediate container and carton labels been provided?	X		

J. BIOPHARMACEUTICS FILING PARAMETERS				
	Parameter	Yes	No	Comment
33.	Does the application contain dissolution data?	X		The following dissolution method is proposed for the quality routine testing: USP 2 (paddle with sinker), 75 rpm, diluted McIlvaine Buffer pH 6 + 0.5 % SLS, 900 mL
34.	Is the dissolution test part of the drug product specifications?	X		The Applicant proposed Q= (b) (4) % in 75 minutes The acceptability of the proposed acceptance criterion will be a review issue.

35.	Does the application contain the dissolution method development report including data supporting the discriminating ability?	X		The Applicant provided dissolution data to support the discriminating ability of the dissolution method; however, the adequacy of the data will be a review issue.
36.	Is there a validation package for the analytical method and dissolution methodology?	X		
37.	Does the application include a biowaiver request?		X	
38.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development?		X	
39.	Are there any formulation and/or manufacturing changes implemented to the clinical formulation? If yes. Are data supporting the bridging between the clinical and commercial drug products and/or manufacturing sites?	X		The proposed commercial formulation is the same as the formulation that was used in Phase 3 clinical studies; except for the capsule shells, which are different in color and imprint from those for commercial capsules. Therefore, comparative dissolution testing with an appropriate statistical analysis (f2 or other model dependent/independent approach) will be requested to support this change.
40.	Is the proposed drug product a modified release dosage form (e.g., controlled release, delayed release).			N/A
41.	Does the application include an IVIVC model?		X	
42.	Does the application include information/data on the in vitro alcohol dose-dumping potential of the proposed drug product?			N/A
43.	Is there enough information to assess the extended release designation claim?			N/A
44.	Is there any in *vivo* BA or BE study in the submission?	X		BA Study 9766-0010. OCP will review this study.

45.	Is the Biopharmaceutics team responsible of reviewing the *in vivo* BA or BE studies? If yes. • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies)?		X	
46.	Is there any design space proposed using in vitro release as a response variable?		X	
47.	Is the control strategy related to in vitro drug release?			N/A
48.	Does the application contain dissolution data?	X		The following dissolution method is proposed for the quality routine testing: USP 2 (paddle with sinker), 75 rpm, diluted McIlvaine Buffer pH 6 + 0.5 % SLS, 900 mL

K. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
49.	**IS THE PRODUCT QUALITY (CMC AND BIOPHARMACEUTICS) SECTIONS OF THE APPLICATION FILEABLE?**	X		
50.	If the NDA is not fileable from the cmc and biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A
51.	Are there any potential review issues identified?	X		
52.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?	X		There are Biopharmaceutics comments to be conveyed to the Applicant in the 74-Day letter. Refer to page 3 of this document.
53.	Are there any internal comments for the other disciplines?			None

Attachment I

Figure 1 Flow Chart of the Synthesis of BAL8557 drug substance

Attachment II

Table 12 Specification for Drug Substance

Attribute	Method	Acceptance Criteria
Description	Visual observation	White to yellowish white powder or powder (b) (4)
Identification (1) HPLC	HPLC	Conforms to reference standard.
(2) Infrared spectrum	USP <197A>	Conforms to the reference spectrum. (difference at about (b) (4) cm^{-1} are expected due to different concentrations of sulfate)
pH in 1.0 % (w/v) aqueous solution	USP <791>	(b) (4)
Appearance of solution (1% acid solution)	USP <631>, <641>	(b) (4)
Heavy metals	USP <231>, Method II	Not more than (b) (4) ppm
Related substances	HPLC	(b) (4) BAL8728: ≤ (b) (4) % (b) (4) BAL4815: (b) (4) % (b) (4)
BAL19714	HPLC (MS/MS)	Not more than (b) (4) ppm
2-Butenal	HPLC	Not more than (b) (4) ppm
Enantiomer	HPLC	Less than (b) (4) %
Residual solvent	GC	(b) (4)
(b) (4)	GC	(b) (4) (b) (4)
(b) (4)	IC	
Water (Karl Fischer)	USP <921>, Method Ic	Not more than (b) (4) %
Residue on ignition	Harmonized test method USP <281>	Not more than %
Bacterial endotoxin	Harmonized test method USP <85>	Less than (b) (4) EU/mg
Microbial limit test	Harmonized test method USP <61>	(b) (4) TAMC: cfu/g TYMC: cfu/g
Assay	HPLC	(b) (4) % to (b) (4) %

TAMC: Total Aerobic Microbial Count, TYMC: Total Combined Yeasts and Molds Count.

Attachment III

Table 1 Composition of Isavuconazonium Sulfate Capsules

Components	Reference Quality Standard	Function	Quantity (mg/capsule)
Isavuconazonium sulfate	In house	Drug substance	186.3 (corresponding to 100 isavuconazole)
Magnesium citrate	USP	(b) (4)	
Microcrystalline cellulose	NF		
Talc	USP		
Colloidal silicon dioxide	NF		
Stearic acid	NF		
(b) (4)			(b) (4)
Capsule (size #0 elongated)	-	Capsule shell	
Ink (b) (4)	-	Ink	
Total capsule weight (mg)			**695.9**

USP: United States Pharmacopeia, NF: National Formulary

(b) (4)

Attachment IV

Figure 2 Manufacturing Process Flow Diagram of Isavuconazonium Capsules

Attachment V

Table 15 Specifications for Isavuconazonium Capsules

Attributes	Methods	Acceptance Criteria
Description	Visual observation	Capsule containing white to yellow powder or powder (b) (4) (b) (4) and consisting of: Cap: White, imprinted in black with "ISA" Body: Swedish orange (reddish-brown color), imprinted in black with the Astellas logo (✈)
Identification	1) HPLC	The retention times of the main peak in the sample and standard chromatograms correspond.
	2) HPLC-PDA	The UV spectra of the main peak in the sample and standard chromatograms correspond.
Related substances	HPLC	(b) (4) : NMT (b) (4) % : NMT % BAL8728 : NMT % (b) (4) : NMT % : NMT % : NMT %
BAL4815	HPLC	NMT (b) (4) %
2-Butenal	HPLC	NMT ppm
Uniformity of dosage units	USP<905> Weight Variation	Conforms
Dissolution	USP<711> Apparatus 2	Q = (b) (4) % in 75 minutes
(b) (4)	(b) (4)	NMT (b) (4) %
Microbial limit [1)]	USP<61> USP<62>	TAMC: (b) (4) cfu/g TYMC: cfu/g *E. coli.*: Absent
Assay	HPLC	NLT (b) (4) % and NMT (b) (4) %

NMT = not more than, NLT = not less than
HPLC-PDA = High Performance Liquid Chromatography-Photodiode Array
TAMC: Total Aerobic Microbial Count, TYMC: Total Combined Yeasts and Molds count

(b) (4)

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page}
Dorota Matecka, Ph.D.
CMC Lead
Division II
Office of New Drug Quality Assessment

{See appended electronic signature page}
Banu Zolnik, Ph.D.
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Office of New Drug Quality Assessment

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Office of New Drug Quality Assessment

{See appended electronic signature page}
Moo-Jhong Rhee, Ph.D.
Branch Chief
Division II
Office of New Drug Quality Assessment

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

/s/

DOROTA M MATECKA
09/04/2014

BANU S ZOLNIK
09/04/2014

ELSBETH G CHIKHALE
09/04/2014

MOO JHONG RHEE
09/05/2014
Chief, Branch IV

Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **207501**

2. DATES AND GOALS:

Letter Date: July 8, 2014	Submission Received Date: July 8, 2014
PDUFA Goal Date: March 8, 2015	

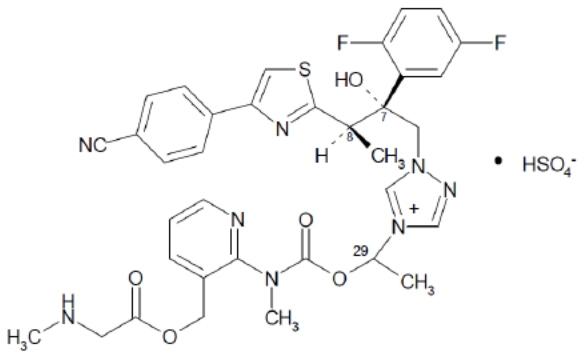
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	CRESEMBA® *(proposed)*
Established or Non-Proprietary Name (USAN):	Isavuconazonium sulfate
Dosage Form:	Powder for injection
Route of Administration	Intravenous
Strength/Potency	372.6 mg isavuconazonium sulfate (equivalent to 200 mg isavuconazole)
Rx/OTC Dispensed:	Rx

4. INDICATION:

Treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older.

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



Molecular Formula: $C_{35}H_{35}F_2N_8O_5S \cdot HSO_4$

Molecular Weight: 814.84†

Molecular Weight of Active Moiety (isavuconazole): 437.47†

6. NAME OF APPLICANT (as indicated on Form 356h):

Astellas Pharma US Inc.

7. SUBMISSION PROPERTIES:

Review Priority:	Priority (PDUFA V)
Submission Classification (Chemical Classification Code):	1
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DAIP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology			*TBD*
Establishment Evaluation Request (EER)		X	Submitted August 7, 2014
Pharmacology/Toxicology	X		
Methods Validation	X		Submitted on August 18, 2014
Environmental Assessment		X	Categorical exclusion claim
CDRH			N/A
Other			N/A

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? **Yes**
CMC Filing Issues:
N/A

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? **No**
CMC Comments for 74-Day Letter:
N/A

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? **Yes**
Biopharmaceutics Filing Issues:
N/A

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? **No**
Biopharmaceutics Comments for 74-Day Letter:
N/A

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? **Yes**
Microbiology Filing Issues:
See Microbiology Filing Review for details and for any potential Microbiology review issues.

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
	X		

Is a team review recommended?	Yes
Suggested expertise for team:	
Quality (CMC, Microbiology and Biopharmaceutics) Review Team: *Gene Holbert, Ph.D. (drug substance reviewer)* *Nina Ni, Ph.D. (drug product reviewer)* *Vinnie Pawar, Ph.D. (product quality microbiology reviewer)* *Banu Zolnik, Ph.D. (biopharmaceutics reviewer)*	

Summary of Critical Issues and Complexities

This NDA provides for an IV formulation (sterile powder for injection) of a new synthetic antifungal drug, isavuconazonium sulfate. It should be noted that this applicant has submitted a concurrent NDA for an oral dosage form of isavuconazonium sulfate, capsules (NDA 207500). CMC information for the drug substance has been included in NDA 207500. For summary of the proposed drug substance, isavuconazonium sulfate and the drug product for an oral administration (isavuconazonium hard capsules) refer to the filing review for NDA 207500 in DARRTS.

A brief summary of the proposed drug product for IV administration in the current NDA is provided in the IQA below. The most critical issue for this NDA will be the precipitate formation in the infusion solutions of the isavuconazonium sulfate, and the proposal by the applicant to use an in-line filter during drug administration. These issues will need to be reviewed in detail and discussed with the NDA review team (particularly with the clinical team) to determine acceptability of this proposal.

Initial Quality Assessment

Isavuconazonium sulfate (BAL8557-002, also referred to as ASP9766) is a water-soluble triazole prodrug. The prodrug is hydrolyzed *in vivo* by plasma esterases to form BAL4815 (isavuconazole, the active moiety), and BAL8728 (an inactive cleavage product). Isavuconazole acts by inhibiting sterol 14-alpha-demethylase, a microsomal P450 enzyme essential for ergosterol biosynthesis in fungi. Isavuconazole demonstrates good in vitro activity against *Aspergillus* spp., Mucormycetes, *Candida* spp. and numerous other filamentous fungi, yeasts and dimorphic fungi. Isavuconazonium is indicated for the treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older.

Isavuconazonium compound was specifically developed to facilitate intravenous administration, without the need for nephrotoxic excipients such as cyclodextrin. Isavuconazonium is available for administration parenterally via intravenous infusion as powder for concentrate for solution for infusion and orally as hard capsules. The proposed therapeutic dose of isavuconazonium is expressed in terms of the quantity of the active moiety: isavuconazole. For intravenous infusion, the dosage strength of the sterile lyophilized powder of 372.6 mg isavuconazonium sulfate corresponds to 200 mg isavuconazole per vial. For oral delivery, the dosage strength of the hard capsule formulation of 186.3 mg isavuconazonium sulfate corresponds to 100 mg of isavuconazole. The oral formulation, which is almost completely bioavailable, can be used in place of the intravenous formulation at any time.

Isavuconazole is administered using a loading dose followed by maintenance dosing:

- Loading dose: 200 mg every 8 hours for the first 48 hours via oral or intravenous administration
- Maintenance dose: 200 mg per day via oral or intravenous administration

The intravenous formulation of isavuconazonium sulfate (sterile lyophilized powder for injection) was developed through IND 72593 and the oral formulation (capsules) was developed via IND 119307. In the course of development, isavuconazonium sulfate was granted a Qualified Infectious Disease Product (QIDP) and Orphan Drug designations.

Several meetings were held during the drug development between the applicant and the FDA. The correspondences relevant to CMC activities during the development of these products (as documented in DARRTS) include:

1. Type C meeting on June 6, 2014 (preliminary responses sent June 3, 2014; meeting cancelled by the Sponsor)

2. Pre-NDA meeting on October 29, 2013 (preliminary responses dated October 25, 2013 and meeting minutes dated November 29, 2013)

3. Type C CMC Guidance meeting on January 17, 2012 (preliminary responses dated January 11, 2012 and meeting minutes dated September 26, 2013)

Drug Substance

Refer to IQA for NDA 207500.

Drug Product

Isavuconazonium sulfate for injection is a sterile, lyophilized product containing 372.6 mg isavuconazonium sulfate, corresponding to 200 mg isavuconazole (active moiety, BAL4815) per vial. Other components of the proposed formulation include mannitol and sulfuric acid used to adjust pH as described in the composition table provided in section 3.2.P.1 (reproduced in the Attachment I, below).

The IV formulation of isavuconazole sulfate is to be administered by intravenous infusion after reconstitution with 5.0 mL of water for injection and further dilution with 0.9% sodium chloride solution or 5% dextrose solution. The instructions for use in the labeling state that the infusion solution should be administered through an inline filter (0.2 to 1.2 µm pore size), placed between the infusion bag and patient access. In addition, the reconstituted solution may be stored for up to one hour prior to preparation of the infusion solution. The infusion solution must be stored refrigerated at between 2°C and 8°C, and the patient infusion must be completed within 24 hours after reconstitution of the lyophilized powder. *Comments: The proposed labeling statements and in-use stability data will need to be evaluated in collaboration with the Product Quality Microbiology Reviewer. Also, see Additional Comments, below, regarding the particulate formation in infusion solutions of isavuconazole sulfate and the proposed use of an in-line filter.*

The manufacturing process of isavuconazonium sulfate for injection consists of the following steps: (b) (4) (see Attachment II, below). The commercial target batch size is (b) (4) and it can vary based on the (b) (4)
Comment: The manufacturing process and other aspects of the proposed drug products such as sterility will be also evaluated by the Product Quality Microbiology Reviewer. It should be noted that the filing review was placed in DARRTS by Dr. Vinnie Pawar and this NDA was determined fileable from the product quality microbiology perspective with no issues for 74-day letter (see review in DARRTS dated August 8, 2014).

The container closure system for the drug product consists of 10 mL vial, 20 mm stopper and 20 mm aluminum/flip-off seal. Information on the proposed container closure system is provided in the pharmaceutical development and container closure sections of 3.2.P. In addition, two Type III DMFs are referenced for individual packaging components. *Comment: The proposed container closure system should be evaluated for safety, compatibility and suitability; for example, was there any evaluation of potential extractables and leachables conducted?*

The drug product stability information submitted in the NDA includes up to 18 months stability data for three registration batches. The three batches tested in the registration stability studies were manufactured at the intended commercial manufacturing site, (b) (4) with the intended commercial manufacturing process on the

commercial scale, and packaged in type I glass vial with rubber stopper. Based on the stability data and the statistical analyses, the initial shelf life of 24 months is proposed for isavuconazonium IV drug product when stored in a refrigerator. *Comment: The proposed expiration dating will need to be assessed based on the overall data provided.*

Additional Comments: One of the most critical issues for this NDA and the proposed drug product is the particulate formation in the diluted solution of isavuconazole sulfate. As a consequence, the infusion solutions of the isavuconazole sulfate fail the USP <788> requirements for particulate matter. This issue was previously discussed with the applicant and it was stated by the Agency that the failure of particulate matter test is a safety concern (refer to the pre-NDA meeting minutes dated November 29, 2013 in DARRTS). The applicant has identified the precipitate as the active moiety (BAL4815) present as an impurity in the lyophilized powder. The pharmaceutical development section includes a report containing data on characterization and identification of the precipitate as well as explanation for its formation. The applicant's proposal is to include a statement in the labeling of this product recommending the use of an in-line filter during the product administration. Since the precipitate formation in an infusion solution is a safety concern, this issue along with all the information provided, along the applicant's proposal of in-line filter use should be carefully evaluated and consulted with the NDA review team, particularly with the clinical team.

Risk Assessment

Product attribute/ CQA	Factors that can impact the CQA	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment, if any
Assay for Isavuconazonium Sulfate	Quality of the incoming API; DP storage; Analytical procedure	3	3	1	9	Evaluate the in-coming material specification and COA provided; evaluate the assay method
Physical stability (solid state)	Stability; (b) (4) Manufacturing process	3	2	4	24	Any potential for solid state changes?
Uniformity of Dosage Units	Assay analytical procedure; Manufacturing process	1	3	1	3	In process control of filling weight
Impurities/degradation products including	Quality of API (large number of impurities); Manufacturing	4	4	4	64	Evaluate control strategy for genotoxic impurities and

extractables and leachables	processes; Raw materials; Container closure (stopper); DP storage;					other impurities; see CoAs for excipients; any testing per <467>? Consult Pharm/Tox Reviewer
Sterility	Manufacturing processes, (b) (4) Container closure	5	5	3	75	Consult Biopharmaceutics Reviewer
Particulate Matter	Manufacturing process; Diluent	5	5	4	100	Evaluate proposed filter use; Consult with Clinical Team

RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)

Initial Quality-Biopharmaceutics Assessment

Biopharmaceutics Synopsis, Critical Issues or Complexities
Submission: This 505 (b)(1) NDA submission is proposing isavuconazonium sulfate sterile lyophilized powder for intravenous infusion.
Introduction: Isavuconazonium sulfate is a water-soluble triazole prodrug. Following i.v. administration isavuconazonium is hydrolyzed to the active drug, isavuconazole (aka BAL 4815). Isavuconazole acts by inhibiting sterol 14-alpha-demyhlase, a microsomal p450 enzyme essential for ergosterol biosynthesis in fungi. Isavuconazonium is indicated for the treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older.
Drug Product Description: Isavuconazonium sulfate is an amorphous material and solubility of the drug substance is reported to be [redacted] (b) (4) The Applicant states that isavuconazonium is [redacted] (b) (4) Isavuconazonium sulfate is formulated as a sterile, lyophilized product containing 372.6 mg isavuconazonium sulfate corresponding to 200 mg isavuconazole per vial. It is administered by iv infusion after reconstitution with 5 mL water for injection and further dilution with a 0.9% sodium chloride solution. The Applicant submitted bioavailability study No. 9766-CL-0010 following single oral and intravenous administration of isavuconazonium sulfate. This study will be reviewed by the Office of Clinical Pharmacology (OCP). The Applicant considers that the oral formulation under NDA 207500 can be used in place of the intravenous formulation under NDA 207501 at any time, because the mean absolute bioavailability of isavuconazole is 98% following a single dose oral administration.
Filing Recommendation: From Biopharmaceutics perspective, this NDA 207501 isavuconazonium sulfate powder for injection, 200 mg is **fileable.** Since there is no biopharmaceutics information to be reviewed in this NDA, no further action is warranted from ONDQA-Biopharmaceutics.

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	X		

	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)			*N/A*

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		*Categorical exclusion claim*

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		*Reference to NDA 207500*
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		*Reference to NDA 207500*
14.	Does the section contain information regarding the characterization of the DS?	X		*Reference to NDA 207500*
15.	Does the section contain controls for the DS?	X		*Reference to NDA 207500*
16.	Has stability data and analysis been provided for the drug substance?	X		*Reference to NDA 207500*
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			*Reference to NDA 207500*
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			*Reference to NDA 207500*

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		Example of executed batch records in 3.2.R.1
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
24.	Does the section contain controls of the final drug product?	X		
25.	Has stability data and analysis been provided to support the requested expiration date?	X		
26.	Does the application contain Quality by Design (QbD) information regarding the DP?			*QbD elements (CQAs, DoEs, risk assessment, control strategy)*
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			*Not immediately obvious (but not required either)*

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
28.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	X		

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III		(b) (4)	9/4/2014*	
	III			6/23/2014	

**LoA was obtained by email by the PM; will be submitted officially to the NDA*

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
31.	Has the draft package insert been provided?	X		
32.	Have the immediate container and carton labels been provided?	X		

Biopharmaceutics Filing Review Checklist

J. Biopharmaceutics FILING PARAMETERS				
	Parameter	**Yes**	**No**	**Comment**
33.	Does the application contain dissolution data?		X	The proposed drug product is lyophilized powder for injection.
34.	Is the dissolution test part of the drug product specifications?	-	-	NA
35.	Does the application contain the dissolution method development report including data supporting the discriminating ability?	-	-	NA

36.	Is there a validation package for the analytical method and dissolution methodology?	-	-	NA
37.	Does the application include a biowaiver request?	-	-	NA
38.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development?	-	-	NA
39.	Are there any formulation and/or manufacturing changes implemented to the clinical formulation? If yes. Are data supporting the bridging between the clinical and commercial drug products and/or manufacturing sites?	-	-	NA
40.	Is the proposed drug product a modified release dosage form (e.g., controlled release, delayed release).	-	-	NA
41. b	Does the application include an IVIVC model?		X	
42.	Does the application include information/data on the in vitro alcohol dose-dumping potential of the proposed drug product?	-	-	NA
43.	Is there enough information to assess the extended release designation claim?	-	-	NA
44. d	Is there any in *vivo* BA or BE study in the submission?	X		Study 9766-0010. OCP will review this study.
45.	Is the Biopharmaceutics team responsible of reviewing the *in vivo* BA or BE studies? If yes. • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies)?		X	
46.	Is there any design space proposed using in vitro release as a response variable?		X	
47.	Is the control strategy related to in vitro drug release?	-	-	NA

K. BIOPHARMACEUTICS FILING CONCLUSION AND COMMENTS				
	Parameter	**Yes**	**No**	**Comment**
48. .	**IS THE PRODUCT QUALITY (CMC AND BIOPHARMACEUTICS) SECTIONS OF THE APPLICATION FILEABLE?**	X		
49.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	-	-	NA
50.	Are there any potential review issues identified?		X	
51.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?		X	.
52.	Are there any internal comments for the other disciplines?			None

Attachment I

Table 1 Unit Composition of Isavuconazonium Sulfate for Injection

Component	Reference Quality Standard	Function	Quantity per vial (mg)
Isavuconazonium sulfate	In house (Section 3.2.S.4.1)	Drug substance	372.6 (corresponding to 200 isavuconazole)
Mannitol	USP	Bulking agent	96.0
Sulfuric acid	NF	pH adjusting agent	(b) (4)
Water for Injection	USP	(b) (4)	(b) (4)
(b) (4)	NF	(b) (4)	
Primary Packaging			
Type I glass vial	In house (Section 3.2.P.7)	Container	one
(b) (4) rubber, (b) (4) (b) (4)	In house (Section 3.2.P.7)	Stopper	one
Aluminum flip-off caps	In house (Section 3.2.P.7)	Seal	one

The amount of isavuconazonium sulfate per vial will be adjusted based on (b) (4) *sulfuric acid is added as necessary for pH adjustment.* (b) (4)

Attachment II

Figure 1 **Manufacturing process flow diagram of isavuconazonium sulfate for injection**

(b) (4)

Attachment III

Table 1 Specifications for Isavuconazonium iv Drug Product

Attributes	Methods	Acceptance Criteria
Description	Visual observation	(b) (4) White to yellow (b) (4) Reconstituted solution: Clear, colorless to yellowish liquid
Identification	1) HPLC	The retention times of the main peak in the sample and standard chromatograms correspond.
	2) HPLC-PDA	The UV spectra of the main peak in the sample and standard chromatograms correspond.
pH	USP <791>	(b) (4) (b) (4)
Related substances	HPLC	: NMT % : NMT % BAL8728 : NMT % (b) (4) : NMT % : NMT % : NMT %
BAL4815	HPLC	NMT (b) (4) %
2-Butenal	HPLC	NMT ppm
Water	USP<921> Method Ic Coulometric Titration	NMT %
Bacterial Endotoxins	USP <85>	LT (b) (4) EU/mg
Uniformity of dosage units	USP<905> Weight Variation	Conforms
Foreign matter	Visual observation	Practically free from visible particles
Particulate matter	USP <788>	(b) (4) µm: NMT (b) (4) /container µm: NMT container
Sterility	USP <71>	Conforms
Assay	HPLC	NLT (b) (4) % and NMT (b) (4) %

NMT = not more than, NLT = not less than, LT = less than, EU = endotoxin units

HPLC-PDA = High Performance Liquid Chromatography-Photodiode Array

(b) (4)

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page}
Dorota Matecka, Ph.D.
CMC Lead
Division II
Office of New Drug Quality Assessment

{See appended electronic signature page}
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DOROTA M MATECKA
09/04/2014

BANU S ZOLNIK
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MOO JHONG RHEE
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