CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208901Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

NDA 208901 Resubmission 3
Review 1

Drug Name/Dosage Form	Tolsura (itraconazole) Capsule
Strength	65 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Mayne Pharma International Pty Ltd
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission/After Refusal to File	*02/16/2018*	*All*
Quality Amendment	*06/27/2018*	*Drug Product*
Quality Amendment	*06/28/2018*	*Process/Facilities*
Quality Amendment	*07/19/2018*	*Biopharm*
Quality Amendment	*07/30/2018*	*Drug Product*
Quality Amendment	*09/07/2018*	*Drug Product*
Quality Amendment	*09/18/2018*	*Biopharm/Process*
Quality Amendment	*09/20/2018*	*Drug Substance*
Quality Amendment	*09/24/2018*	*Drug Product*
Quality Amendment	*09/27/2018*	*Drug Product/Biopharm*
Quality Amendment	*10/04/2018*	*Process*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Haripada Sarker	Su Truong
Drug Product	Yong Wang	Balajee Shanmugam
Process	Sateesh Sathigari	Upinder Atwal
Facility	Sateesh Sathigari	Upinder Atwal
Biopharmaceutics	Joan (Zhuojun) Zhao	Elsbeth Chikhale
Regulatory Business Process Manager	Anh-Thy Ly	

Application Technical Lead	Yushi Feng	
Laboratory (OTR)	N/A	
ORA Lead	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	See DS review				
	Type III	See DP review				

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for APPROVAL from the product quality perspective.

II. Summary of Quality Assessments

A. Product Overview

The drug product, Tolsura (itraconazole) Capsules 65 mg, is an immediate release powder-filled capsule indicated for the treatment of several fungal infections in immunocompromised and non-immunocompromised patients.

Proposed Indication(s) including Intended Patient Population	Tolsura (itraconazole) Capsules 65 mg is indicated for the treatment of several fungal infections in immunocompromised and non-immunocompromised patients.
Duration of Treatment	Not specified
Maximum Daily Dose	260 mg daily
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

The listed drug (LD) for this 505(b)(2) NDA is Janssen Pharmaceuticals Inc's Sporanox® (itraconazole) capsules, 100 mg (NDA 20083). The original NDA for itraconazole capsules (b) (4) 65 mg was submitted on November 30, 2015, and was refused to file (RTF) in January 2016, due to several clinical and clinical pharmacology deficiencies such as an insufficient exposure bridge to the LD and lack of clinical data to support efficacy for the proposed indications (refer to the RTF letter dated January 29, 2016). In the current resubmission, the Applicant only seeks approval for the 65 mg itraconazole capsules (b) (4) (b) (4) The clinical basis for this NDA relies on PK bridging between the sponsor's proposed 65 mg capsule versus Sporanox® capsule, 100 mg.

Drug Substance:
The CMC information of the drug substance are cross-referenced to DMF (b) (4) and DMF (b) (4) Both the DM (b) (4) and DMF (b) (4) had been reviewed to be Adequate. Subsequent amendments were evaluated during this review and also found adequate, and thereby the DS part is found Satisfactory to support the NDA 208901.

For additional details, see the Drug Substance review below.

Drug Product:
SUBA™-Itraconazole 65 mg Capsules are formulated as immediate release capsules. (b) (4) encapsulated into hard gelatin capsules. Itraconazole drug substance complies with the official USP and Ph. Eur. monographies. Compendial excipients are used in the manufacture of the proposed drug products except for gelati (b) (4) Gelatin capsules are manufactured by a well-established manufacturer (b) (4) The capsule specifications from the manufacturer and the applicant are acceptable.

Based on the control strategy, stability data, post approval stability commitments, this NDA is considered adequate to assure the identity, strength, purity, and quality.

The shelf-life and storage conditions for itraconazole capsules 65 mg are listed below.

- For itraconazole capsules 65 mg stored in the proposed HDPE bottles, the proposed shelf-life of 36 months is acceptable if stored at controlled room temperature 15°-25°C (59°-77°F) and protected from light and moisture.
- (b) (4)

For additional details, see the Drug Product review below.

Process:
(b) (4)

(b) (4)

Facilities:

(b) (4)

Biopharmaceutics:

The Biopharmaceutics review evaluates the proposed dissolution method, the dissolution acceptance criterion, and the need for bridging.

Based on the provided dissolution data, the following dissolution method and the revised dissolution acceptance criterion are acceptable and agreed upon:

Proposed Dissolution Method	
Apparatus	USP II (Paddle)
Rotation Speed	75 RPM
Medium	0.5% SLS in water
Volume	900 mL
Acceptance Criterion	Q (b) (4) % at 30 minutes

The formulation, image and manufacturing site for the clinical and stability batches 961007, 967722 and 263862 are the same as the proposed formulation, image, and manufacturing site for commercial manufacture. The Applicant has provided supportive information to bridge the two API sources.

For additional details, see the Biopharmaceutics review below.

Environmental Assessment:
The claim of categorical exclusion per 21 CFR 25.31(a) is acceptable.

For additional details, see the Drug Product review below.

C. Special Product Quality Labeling Recommendations (NDA only)

Recommendations have been conveyed to the OND PM for consideration as the labeling is finalized. See the OPQ Labeling review below.

D. Final Risk Assessment (see Attachment)

Yushi Feng

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Final Risk Table

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations/ Comments**
Assay/Stability		L		Acc	
Physical stability		M	(b) (4)	Acc	
Content uniformity		L		Acc	
Dissolution		M		Acc	
Microbial limits		L		Acc	

Yushi Feng

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LABELING

IQA Review Guide Reference

NDA 208901

I. Package Insert

1. *Highlights of Prescribing Information*

These highlights do not include all the information needed to use TOLSURA (b) (4) safely and effectively. See full prescribing information for TOLSURA (b) (4)
TOLSURA (itraconazole capsules), for oral use
Initial U.S. Approval: <<Insert four-digit year>>

DOSAGE FORMS AND STRENGTHS
Capsules: 65 mg (3)

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	TOLSURA (itraconazole capsules)
Dosage form, route of administration	For oral use
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Capsules: 65 mg

2. *Section 2 Dosage and Administration*

2.1. Treatment of Blastomycosis and Histoplasmosis

The recommended dose is 130 mg once daily (2 x 65 mg capsules) (b) (4)
I (b) (4) no obvious improvement, or there is evidence of progressive fungal disease, the dose should be increased in 65-mg increments to a maximum of 260 m (b) (4) Doses above 130 mg/day should be given in two divided doses.

2.2. Treatment of Aspergillosis

(b) (4)

2.3. Treatment in Life-Threatening Situations

(b) (4)

Although clinical studies did not provide for a loading dose, it is recommended, based on pharmacokinetic dat (b) (4) a loading dose of 130 mg (2 x 65 mg capsules) three times daily (390 mg/day) *be give* (b) (4) for the first 3 day (b) (4) (b) (4)

Treatment should be continued for a minimum of three months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	(b) (4) *with food*

3. *Section 3 Dosage Forms and Strengths*

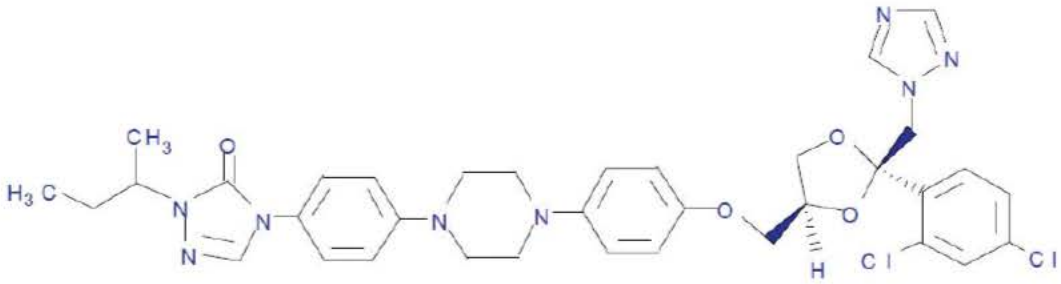
TOLSURA (b) (4) (itraconazole capsules) is available in a size 1, hard gelatin capsules with light blue cap and white body, imprinted with "i-65" in black on the cap and containing 65 mg of itraconazole (b) (4) (b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Capsules
Strengths: in metric system	containing 65 mg of itraconazole
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Capsules are available in a size 1, hard gelatin capsules with light blue cap and white body, imprinted with "i65" in black on the cap…

4. *Section 11 Description*

TOLSURA (b) (4) itraconazole, an azole antifunga (b) (4) Itraconazole is an equal mixture of four diastereomers (two enantiomeric pairs), e ossessing three

chiral center (b) (4) (b) (4) It may be represented by the following structural formula and nomenclature:



(±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[[(2R*,4S*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one mixture with (±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[[(2S*,4R*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one

or

(±)-1-[(RS)-sec-butyl]-4-[p-[4-[p-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one.

Itraconazole has a molecular formula of $C_{35}H_{38}Cl_2N_8O_4$ and a molecular weight of 705.64. It is a white to slightly yellowish powder. It is insoluble in water, very slightly soluble in alcohols, and freely soluble in dichloromethane. It has a pKa of 3.70 (based on extrapolation of values obtained from methanolic solutions) and a log (n-octanol/water) partition coefficient of 5.66 at pH 8.1.

(b) (4) Each capsule contains 65 mg of itraconazole. Inactive ingredients ar (b) (4) hypromellose phthalate, sodium starch glycolate, colloidal silicon dioxide and magnesium stearate.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	TOLSURA Itraconazole
Dosage form and route of administration	Capsules for oral use
Active moiety expression of strength with equivalence statement (if applicable)	65 mg of itraconazole
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Inactive ingredients ar (b) (4) (b) (4) hypromellose phthalate, sodium starch glycolate, colloidal silicon dioxide and magnesium stearate. *Please list names for inactive ingredients in alphabetical order.* The above comment in red has been communicated to the applicant.
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	itraconazole, an azole antifungal agent
Chemical name, structural formula, molecular weight	Available The statement for diastereomers has been discussed and agreed with Drs. Charles Jewell and Haripada Sarker.
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	It has a pKa of 3.70 (based on extrapolation of values obtained from methanolic solutions) and a log (n-octanol/water) partition coefficient of 5.66 at pH 8.1.

5. *Section 16 How Supplied/Storage and Handling*

TOLSURA (itraconazole capsules (b) (4) (b) (4) in a size 1, hard gelatin capsules with light blue cap and white body, imprinted with "i-65" in black on the cap and containing 65 mg of itraconazole.

(b) (4) capsules are supplied in

- bottles of 60 capsules NDC 51862-462-60

(b) (4)

Store at 25°C (77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight, light resistant container (USP).

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	containing 65 mg of itraconazole
Available units (e.g., bottles of 100 tablets)	bottles of 60 capsules (b) (4)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	in a size 1, hard gelatin capsules with light blue cap and white body, imprinted with "i-65" in black on the cap • bottles of 60 capsules NDC 51862-462-60 (b) (4) The above deficiency has been discussed and communicated to
Special handling (e.g., protect from light)	Dispense in a tight, light resistant container (USP).
Storage conditions	Store at 25°C (77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Mayne Pharma Greenville, NC 27834 Made in Spain

Reviewer's Assessment of Package Insert: ***{Adequate/Inadequate}***

The statement for diastereomers has been discussed with Drs. Charles Jewell and Haripada Sarker.

All deficiencies for PI have been discussed and accepted in the labeling meeting dated October 2, 2018. The comments will be communicated to the applicant.

{Assess if the Prescribing Information complies with all regulatory requirements from a CMC perspective}

- ***Any deficiencies should be listed at the end in the "List of Deficiencies"***

II. Labels:

1. *Container and Carton Labels*

(b) (4)

2. *Carton Label*

Not provided

{Copy/paste or refer to a representative example of a proposed carton labels}

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	TOLSURA (Itraconazole Capsules)	
Dosage strength	65 mg Each capsule contains: itraconazole..... 65 mg	
Net contents	60 Capsules	
"Rx only" displayed prominently on the main panel	"Rx only" is displayed prominently on the main panel	
NDC number (21 CFR 207.35(b)(3)(i))	NDC 51862-462-60	
Lot number and expiration date (21 CFR 201.17)	*Not provided*	
Storage conditions	Store at 25°C (77°F); excursions permitted 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container (USP).	
Bar code (21CFR 201.25)	Available	
Name of manufacturer/distributor	Mayne Pharma Greenville, NC 27834 Made in Spain	
And others, if space is available	Usual dosage: See Package Insert for Full Prescribing Information. Keep this and all drugs out of the reach of children.	

Reviewer's Assessment of Labels: ***{Adequate/Inadequate}***

The following should be communicated to the applicant.

Per 21 CFR 201.17, provide spaces for lot number and expiration date for container and carton labels.

For storage conditions, the following is recommended:
Store at 25°C (77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Dispense in a tight, light-resistant container (USP)

{Assess if the labels comply with all regulatory requirements from a CMC perspective}

- ***Any deficiencies should be listed at the end in the "List of Deficiencies"***

List of Deficiencies:

Per 21 CFR 201.17, provide spaces for lot number and expiration date for container and carton labels.

For storage conditions, the following is recommended:

Store at 25°C (77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container (USP)

Overall Assessment and Recommendation:

Primary Labeling Reviewer Name and Date:

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Yong Wang

Digitally signed by Yong Wang
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Balajee Shanmugam

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Date: 10/16/2018 02:16:26PM
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BIOPHARMACEUTICS

Product Background:
NDA: 208901(505(b)(2))

Drug Product Name / Strength (b) (4) (itraconazole) Capsules, 65 mg

Route of Administration: Oral

Applicant Name: Mayn Pharma International Pty Ltd (Mayne Pharma)

Indication: Treatment of several fungal infections in immunocompromised and non-immunocompromised patients.

Review Summary:
This New Drug Application is submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355). The listed drug (LD) is Janssen Pharmaceuticals Inc's Sporanox® (itraconazole) capsules, 100 mg (NDA 20083). The original NDA for itraconazole capsule (b) (4) (b) (4) 65 mg was submitted on November 30, 2016, and was refused to file (RTF) in January 2016, due to several clinical and clinical pharmacology deficiencies such as an insufficient exposure bridge to the LD and lack of clinical data to support efficacy for the proposed indications (refer to the RTF letter dated January 29, 2016). In the current resubmission, the Applicant only seeks approval for the 65 mg itraconazole capsules (b) (4) (b) (4) The clinical basis for this NDA relies on PK bridging between the sponsor's proposed 65 mg capsule versus Sporanox® capsule, 100 mg.

This review evaluates the proposed dissolution method, the dissolution acceptance criterion, and the need for bridging.

Based on the provided dissolution data, the following dissolution method and the revised dissolution acceptance criterion are acceptable and agreed upon:

Proposed Dissolution Method	
Apparatus	USP II (Paddle)
Rotation Speed	75 RPM
Medium	0.5% SLS in water
Volume	900 mL
Acceptance Criterion	Q (b) (4) % at 30 minutes

The formulation, image and manufacturing site for the clinical and stability batches 961007, 967722 and 263862 are the same as the proposed formulation, image, and manufacturing site for commercial manufacture. The Applicant has provided supportive information to bridge the two API sources.

List of Submissions being reviewed:

Submission(s) Reviewed	Document Date
Original	11/30/2015
Resubmission	2/16/2018
IR Response	7/19/2018, 9/18/2018 and 9/27/2018

Review Recommendation:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 208901 fo (b) (4) (itraconazole) Capsules, 65 mg, is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date: Zhuojun Joan Zhao 10/5/2018
Secondary Reviewer Name and Date: Elsbeth Chikhale, Ph.D. 10/9/2018

BCS Designation

The Applicant did not request an official BCS designation. The Applicant considers itraconazole as a drug substance with very low solubility based on the Biopharmaceutical Classification System (BCS).

Drug Substance

The Applicant did not observe polymorphs of the drug substance.

Drug Substance Solubility:

The Applicant states that the drug substance is practically insoluble in water and no solubility data are provided in the NDA.

Formulation:

The Applicant applied the SUBA™ technology to improve the oral absorption of itraconazole (b) (4) (b) (4) (b) (4) The composition of the proposed commercial formulation, an immediate-release capsules is shown in Table 1 below.

Table 1: Qualitative and Quantitative Composition of the Drug Product

Component	Grade	Quantity (mg/capsule)	Function
Itraconazole	USP/Ph.Eur.	(b) (4)	
Hypromellose Phthalate (b) (4)	NF/Ph.Eur.		
Sodium Starch Glycolate (b) (4)	NF/Ph.Eur.		
Colloidal Silicon Dioxide (b) (4) (b) (4)	NF/Ph.Eur.		
Magnesium Stearate (b) (4)	NF/Ph.Eur.		
(b) (4)	NF/Ph.Eur.		
	NF		
Capsule size No 1 (b) (4) Light Blue Cap/White Body	In-house		
(b) (4)	21 CFR		
	21 CFR		
Gelatin	USP/Ph.Eur.		
(b) (4)			
		(b) (4)	

Dissolution Method:

The dissolution method was originally developed (b) (4) (b) (4) for the 65 mg strength. Upon introduction and selection of the dose proportional higher 65 mg strength capsule, the Applicant also verified that the dissolution method is suitable for the proposed 65 mg capsule.

Proposed Dissolution method	
Apparatus	USP II (Paddle)
Rotation (rpm)	75
Medium	0.5% SLS in water
Volume (mL)	900 mL

In the Pharmaceutical Development section (Module 3.2.P.2), justification for the choice of dissolution medium, apparatus, and agitation speed are provided, and summarized below.

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(b) (4)

[redacted]

Review Assessment:

The proposed dissolution method could detect changes (b) (4) [redacted] *. As the Applicant does not propose Tier 2 test in the current submission, the Applicant could conduct Tier II* (b) (4) [redacted] *observed.*

Reviewer's Assessment of the dissolution method and method validation: Acceptable

The Applicant has adequately demonstrated the suitability of the dissolution method for batch release and stability testing.

The dissolution method shows discriminating abili (b) (4) [redacted] *The proposed dissolution method's discriminating power with regards to other critical manufacturing variables was not demonstrated.*

The proposed dissolution method (i.e. US Apparatus II at 75 rpm using 900 mL 0.5% SLS in water) is found acceptable for the QC of the proposed drug product.

Dissolution Acceptance Criterion:

The Applicant initially proposed a dissolution acceptance criterion of Q (b) (4) [redacted] % (b) (4) [redacted] minutes.

Based on the provided dissolution data from pivotal batch 961007 (BA/BE study MPG009) in Table 2 and dissolution data of batch 263862 (BA/BE study MPG013, MPG015 and MPG017)

provided in Appendix 3, a dissolution acceptance criterion of Q (b)(4)% at 30 minutes was recommended in Appendix 5 and agreed upon.

Table 2: Comparative Dissolution Data for the proposed drug product (Itraconazole 65 mg) and the Listed drug (SPORANOX) Products used in Pivotal PK Study MPG009

Product	Batch	Average Drug Release (% Label Claim) by Sample Time (min)					
		5	15	30	45	60	120
SUBA-Itraconazole Capsule 65 mg (test)	961007[1]	36.5	78.5	93.0	96.2	97.2	98.0
Sporanox Capsule 100 mg (RLD)	2LG370	3.2	23.4	56.4	76.7	85.5	97.2

The proposed drug product and the listed drug product showed different in vitro performance using the proposed dissolution method, while the Applicant conducted the following BA/BE studies to support the bridging by in vivo performance, which would be reviewed by OCP reviewer.

Table 3: Primary Studies with Itraconazole Capsules 65 mg against the listed drug

Study Ref	Study Objective	Test Product Lot No. (SUBA®-Itraconazole Capsule 65mg)	RLD Lot No. (Sporanox® Capsule 100mg)
MPG009	Pivotal bio-study (fasted & fed) – once daily dosing	961007	2LG370
MPG012	Steady state study (fed) – once daily dosing	967722	15DG216
MPG013	Steady state study (fed) with loading dose	263862	16BG227
MPG015	Steady state study (fed) – twice daily dosing	263862	16BG227
MPG016	PPI interaction study	263862	Not applicable
MPG017	Food effect study (steady state fed/fasted) – twice daily dosing	263862	Not applicable

Bridging:

The formulation, image, and manufacturing sit (b)(4) for the registration batches 961007 (used in Pivotal Study MPG009), 967722 (used in pivotal study MPG012) and 263862 (used in MPG013, MPG015, MPG016 and MPG017)[2] are the same as the proposed formulation for commercial manufacture.

The Applicant proposes two sources of drug substanc (b)(4) an (b)(4) The drug substance sources are found acceptable from a Biopharmaceutics perspective. The Applicant has provided the following supportive information to bridge the two API sources:

[2] Appendix 4

Drug Substance Site	Reason
(b) (4)	• Drug substance from (b) (4) was used for the clinical batches (Batch No. 959983, 966697 and 244660) and the stability batch No. 966696 for the proposed Itraconazole Capsules 65 mg (b) (4) • The Itraconazole Capsule (b) (4) 65 mg ar (b) (4) filled capsules consisting of (b) (4) (b) (4)

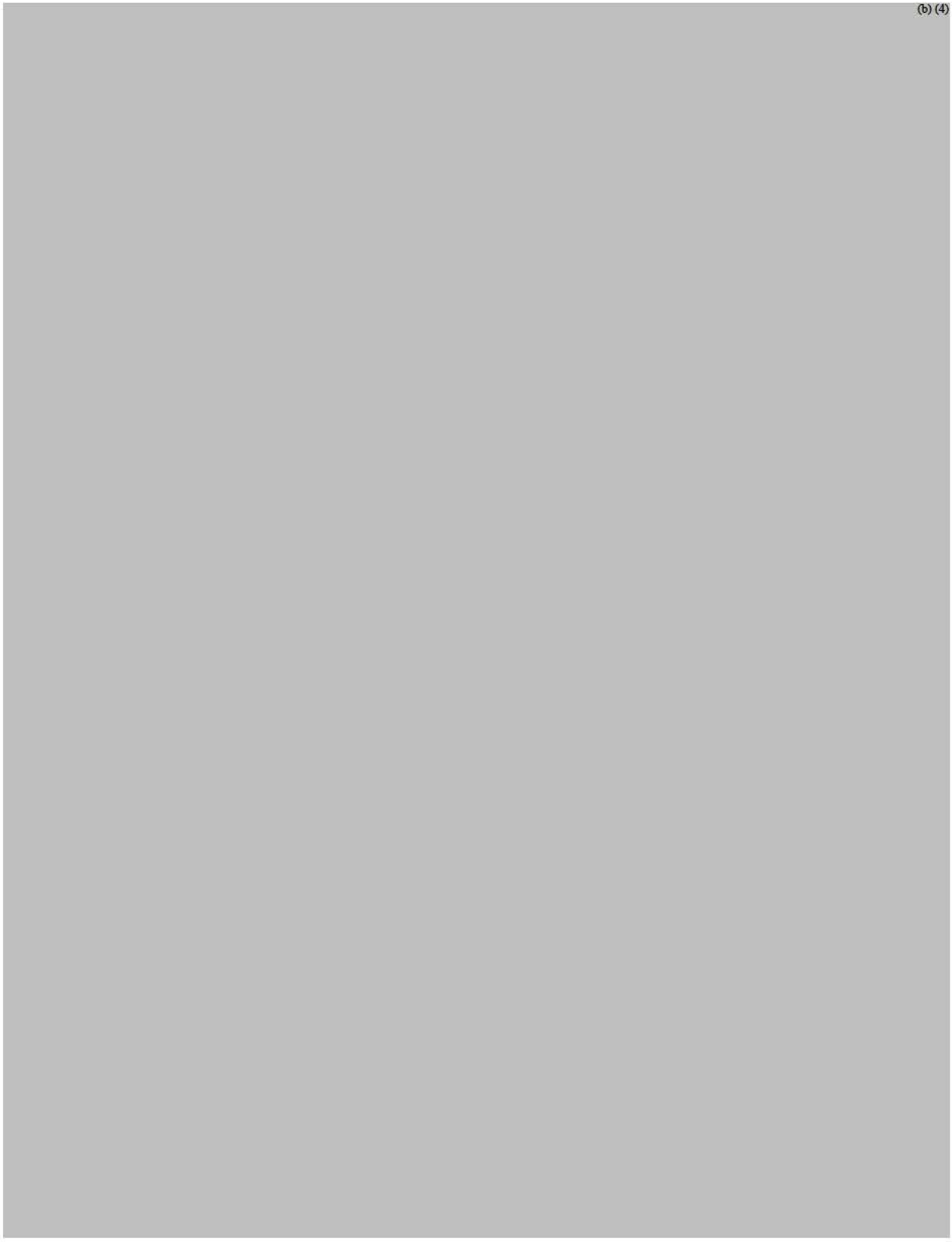
R Regional Information

Comparability Protocols: None

Post-Approval Commitments: None

Lifecycle Management Considerations: None

(b) (4)



APPENDIX 2: *Biopharmaceutics Information Requests Dated June 20, 2018 and Applicant Response Dated July 19, 2018*

Biopharmaceutics Request Comments:

Provide full dissolution profiles for a recent clinical and/or registration batch fo (b) (4) *your drug product using the proposed dissolution conditions and a paddle rotation speed of 50, 60, and 75 RPM. Provide the age and storage condition of the testing batches.*

Applicant's Response to Biopharmaceutics-IR Comment:

(b) (4)

(b) (4) Testing was completed in 0.5% SLS dissolution media, n=12 vessels at 50, 60 and 75 rpm. Batch details are provided below:

Product	Batch	DOM	Expiry	Approximate Age	Storage	Comments
(b) (4)						
SUBA Itraconazole 65 mg Capsules (b) (4)	263862	February 2016	February 2019	2 year, 4 months	25°C/ambient (retention store)	Used in studies MPG013, MPG015, MPG016, MPG017

The Applicant claimed that the dissolution profiles of 65 mg (attached in Appendix 3) demonstrated increase (b) (4)

Reviewer Note:

(b) (4)

The Applicant's proposed rotation speed of 75 rpm is accepted (b) (4)

(b) (4)

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APPENDIX 4: *SUBA Itraconazole Capsules 65 mg Batch Overview*

Capsule Strength	Capsule Batch No.	Active Source	Use	Study References
65 mg	959983 (961007)	(b) (4)	Clinical – BA/BE studies	BA/ BE Study: MPG009 (b) (4)
			Stability	Stability Studies: R2680, R2681
	966696		Stability	Stability Studies: R2697, R2682
	966697 (967722)		Clinical – BA/BE studies	BA/BE Study: MPG012
			Stability	Stability Studies: R2698, R2683
	244660 (263862)		Clinical – BA/BE studies	BA/BE Studies: MPG013, MPG015, MPG017
			Stability	Stability Study: Q3046

APPENDIX 5: *Biopharmaceutics Information Requests Dated September 11, 2018 and Applicant Response Dated September 17, 2018*

Biopharmaceutics Request Comments:

1. Based on the provided dissolution profile data, a dissolution acceptance criterion of Q= (b) (4)% at 30 minutes is recommended for your proposed SUBA (itraconazole) Capsules, 65 mg.

Update your drug product release and stability specifications accordingly. Note that setting of the dissolution acceptance criterion are based on stage 2 testing (n=12) and therefore sometimes stage 2 testing and occasional stage 3 testing may be needed.

2. We could not locate detailed batch information of batch A78- (b) (4) or batch A78-071 (b) (4). Provide detailed information of the comparison of these batches to support the discriminating ability of your proposed dissolution method.

Applicant's Response to Biopharmaceutics-IR Comment 1:

The dissolution specification has been updated to Q (b) (4)% at 30 minutes. 3.2.P.5.1 and 3.2.P.8.2 have been revised accordingly.

Reviewer Assessment:

The Applicant's response is satisfactory.

Applicant's Response to Biopharmaceutics-IR Comment 2:

Comparative dissolution data for the above-mentioned product development batches and the commercial formulation of itraconazole 65mg capsules batch 961007 are provided as Attachment 1.

Reviewer Assessment:

The Applicant provided comparison of dissolution profiles, comparing the registration batch # 961007 to the development batches. However, the Applicant did not provide detailed batch information for the development batches. In order to evaluate the discriminating ability of the proposed the dissolution method, the Agency requested the Applicant provide batch information of those development batches in Appendix 6.

The Applicant's response is inadequate.

APPENDIX 6: *Biopharmaceutics Information Requests Dated September 26, 2018 and Applicant Response Dated September 27, 2018*

Biopharmaceutics Request Comments:

Provide detailed batch information for batch A78-09 (b) (4)*, batch A78-07* (b) (4)*, A78-081-* (b) (4)*, A78-081* (b) (4) *A78-081-* (b) (4) *or A78-081-* (b) (4)*, including form* (b) (4) *), manufacturing date, storage condition, as well as the age of the batch at the time of testing (for dissolution profiles provided in amendment dated 9/18/2018). Provide a table comparing the formulations between these batches and the commercial formulation.*

Applicant's Response to Biopharmaceutics-IR Comment:

The grades of the following four ingredients did not change in any of the abovementioned batches: (b) (4) (b) (4)

(b) (4)

These batches were stored at ambient conditions and tested during product development prior to confirmation of the final formulation.

Details of excipient quantities and (b) (4) used in the various development batches are provided in table 2. Compared with Batch A78-071, the subsequent batches investigated:

- (b) (4)

Table 2: Detailed Information for Product Development Batches

	(b) (4)	Commercial formulation
Date of Manufacture		ongoing
		mg/capsule
Itraconozole		65.00
Hypromellose Phthalate (b) (4)		(b) (4)
Colloidal Silicon dioxide (b) (4)		
Sodium Starch glycolate (b) (4)		
Magnesium Stearate (b) (4)		
Capsules, Size No. 1 (b) (4) Light Blue (b) (4) (b) (4)		

Reviewer Assessment:

The Applicant's response is satisfactory.

APPENDIX 7: *Qualitative and Quantitative Composition*[4]

Component	Grade	Quantity (mg/capsule)	Function
		65 mg Capsule	
Itraconazole	USP/Ph.Eur.	65.00	active
Hypromellose Phthalate	NF/Ph.Eur.		
Sodium Starch Glycolate	NF/Ph.Eur.		
Silicon Dioxide Colloidal	NF/Ph.Eur.		
Magnesium Stearate	NF/Ph.Eur.		
	NF/Ph.Eur.		
Capsule size No 1 Light Blue/	In-house		

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