CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214770Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☒ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 214770
Assessment # 1

Drug Product Name	Noxafil® PowderMix (posaconazole) for delayed-release oral suspension
Dosage Form	Powder for oral suspension
Strength	300 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Merck Sharp & Dohme Corp.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
0000	July 31, 2020	All
0004	September 22, 2020	Facilities
0005	October 27, 2020	Drug Product
0010	December 21, 2020	Microbiology, Process
0011	January 8, 2021	Biopharmaceutics, Drug Product
0012	January 28, 2021	Biopharmaceutics
0013	January 29, 2021	Microbiology
0015	February 3, 2021	Biopharmaceutics
0016	February 11, 2021	Drug Product
0018	February 16, 2021	Biopharmaceutics
0019	March 3, 2021	Process
0020	March 5, 2021	Microbiology
0021	March 12, 2021	Drug Product
0022	March 17, 2021	Microbiology
0023	March 31, 2021	Biopharmaceutics
0024	April 2, 2021	Biopharmaceutics
0035	May 17, 2021	Biopharmaceutics (PMC)

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Rajan Pragani	Ali Al Hakim
Drug Product	Grace Chiou	Thomas Oliver
Manufacturing	Christine Falabella	Jiao Yang
Microbiology	Karthik Krishnan	Yeissa Rosello
Biopharmaceutics	Kevin Wei	Elsbeth Chikhale
Environmental Analysis	Refer to Drug Product Review	
Laboratory (OTR)	N/A	
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Dorota Matecka	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status*	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)		Adequate	9/26/2014	
	III			Adequate	3/19/2004	
	III			Adequate	12/30/2016	
	III			Adequate	9/10/2012	
	III			Adequate	10/4/2013	
	III			Adequate	11/9/2012	
	III			Adequate	4/17/2012	
	III			Adequate	10/3/2007	
	III			Adequate	3/18/2016	

**Refer to the Drug Product Review for details regarding the information provided in the NDA for the container closure system including the status of referenced DMFs*

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	125097	Posaconazole powder for delayed-release suspension
NDA	22003	Posaconazole oral suspension
NDA	205053	Posaconazole delayed-release tablet
NDA	205596	Posaconazole injection

C. CONSULTS: None

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, posaconazole for delayed-release oral suspension. The manufacturing and testing facilities have been found acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on April 27, 2021. Therefore, this NDA is recommended for **approval** by the Office of Pharmaceutical Quality (OPQ).

The following Post-Marketing Commitment (PMC) should be included in the action letter:

PMC 4072-2

Develop a new dissolution method using constituted suspension samples for the Quality Control (QC) testing of the proposed drug product. Submit a method validation report and include additional dissolution data for constituted suspension samples from unexpired batches using 65 rpm and 75 rpm to determine an appropriate paddle rotation speed.

Final Report Submission: 08/2021

The changes in the dissolution method resulting from this PMC study should be submitted to the NDA as a prior-approval supplement before marketing any commercial drug product batches.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Posaconazole is an azole antifungal agent previously approved and commercially available in several dosage forms. This NDA provides for a new formulation, posaconazole powder for delayed release oral suspension, to be used for prophylaxis of invasive Aspergillus and Candida infections in pediatric patients who are at high risk of developing these infections due to being severely immunocompromised, such as HSCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy.

Posaconazole powder for delayed release oral suspension has been developed as delayed release/gastro-resistant formulation. (b) (4)

Posaconazole powder is supplied in sachets. Each sachet contains 300 mg of posaconazole (b) (4). The final drug product is presented as a kit containing the drug component, posaconazole powder in sachets, a suspending vehicle in a bottle, measuring devices (oral syringes), a syringe adapter cap for the suspension vehicle bottle and ancillary components such as mixing cups. Prior to administration, posaconazole powder is dispersed in 9 mL of suspending vehicle to obtain a suspension with a final posaconazole concentration of approximately 30 mg/mL.

The CMC information (including environmental assessment) for the new posaconazole formulation is submitted in the current NDA (Module 3). The results of the clinical study including an updated labeling information, i.e., a revised package insert that combines information for posaconazole tablets, oral suspension, injection and the current formulation, a powder for delayed-release oral suspension, are provided in the efficacy supplement NDA 205596/S-012. For completion, the OPQ review of the labeling submitted in the efficacy supplement is included in this review.

Proposed Indication(s) including Intended Patient Population	Prophylaxis of invasive Aspergillus and Candida infections in adults and pediatric patients aged 2 – 18 years of age who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.
Duration of Treatment	Varies – up to 14-day treatment (refer to the Package Insert for details).
Maximum Daily Dose	*To be determined (currently 240 mg)*
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The posaconazole drug substance used in the current drug product, posaconazole for delayed-release oral suspension, is manufactured using the same drug substance process and controls developed and approved under NDA 22003 (posaconazole oral suspension, 40 mg/mL). Therefore, the CMC information for the drug substance for the current NDA has been provided via a cross-reference to NDA 22003.

NDA 22003 was approved on September 15, 2006. The most recent supplement to NDA 22003 containing drug substance information was Supplement #23, which was reviewed and approved on March 13, 2018. No other significant drug substance information has been submitted since that supplement. Therefore, the cross-referenced drug substance information in NDA 022003 is considered adequate to support the drug substance to be used in the drug product under the current NDA.

Refer to the Drug Substance Memorandum, below.

Drug Product: Adequate

The drug product is a kit containing eight (8) sachets of posaconazole powder, one (1) bottle of suspending vehicle, mixing cups, measuring devices (oral notched tip syringes), and a syringe adapter cap for the suspension vehicle bottle, all co-packaged in a specially designed cardboard carton.

The drug component of the kit, posaconazole powder for delayed-release oral suspension (PFS) is supplied in sachets, each containing 300 mg of posaconazole. There is only one excipient used in the powder formulation, hypromellose acetate succinate, which is a compendial excipient. Prior to administration, the powder is reconstituted in the suspending liquid to deliver a 30 mg/mL oral suspension. The suspending vehicle (b) (4) contains a number of excipients; however, it does not contain the dyes. The suspending vehicle does not include any novel excipients and most of the excipients are compendial. For those excipients, which are non-compendial, adequate quality information was provided in the NDA.

The specifications for both components of the kit, posaconazole PFS and the suspending vehicle, include all relevant quality attributes to assure identity, strength, quality, purity, and potency. These tests include description, preservative identification and assay, pH, specific gravity, and microbial controls for the suspending vehicle. For posaconazole PFS, the

quality attributes include description, identification, assay, degradation products, uniformity of dosage units, dissolution, and microbiological quality. The tests for suspendability (b) (4) have not been proposed for routine testing; however, the rationale and justifications for exclusion these tests from the posaconazole powder specification provided by the Applicant in the initial NDA submission and subsequent amendments, were found sufficient and adequate by the Drug Product Reviewer.

Information provided regarding elemental impurities following the ICH Q3D and USP <232> recommendations, was also found acceptable. Based on the risk assessment and testing data provided, there is minimal risk to patient safety regarding elemental impurities in the drug product.

The overall information provided for the container closure systems for both, posaconazole powder and the suspending vehicle, which includes material information, appropriate CFR citations, references to applicable DMFs Type III, stability data, etc., has been found adequate to demonstrate that these container closure systems (the laminate sachets and HDPE bottles, respectively) are suitable for their intended use.

The drug product information included the results of the dose accuracy study, which was conducted to demonstrate that the notched tip syringes included in the kit can deliver an accurate volume of the suspension (up to 10 mL). However, the assessment of the kit sample conducted by DMEPA and the results of the Human Factor (HF) studies provided in the NDA revealed that only up to 8 mL of the suspension (up to 240 mg of posaconazole) could be consistently and accurately withdrawn by patients using the instructions described in the labeling. These results were discussed extensively by the NDA review team and with the Applicant. Because, from a clinical perspective, the largest volume of the suspension (10 mL, 300 mg of posaconazole) would be needed for children who weigh over 40 kg, it was agreed that the Applicant will perform further studies to develop an appropriate administration method of the suspension for this group of patients via a post-marketing commitment (PMC). This PMC study would also need to generate data to demonstrate that the entire dose (300 mg) can be delivered to these patients using the proposed method of administration. The details and timelines of this PMC study are currently under discussion with the Clinical and DMEPA teams. The OPQ team will participate in the assessment of this PMC study when the protocol and the study results are submitted.

The stability information submitted in the NDA supports the proposed 36 months expiry for the drug product to be stored at controlled room temperature. In addition, in-use stability data were provided to support the

storage statements included in the package insert, Dosage and Administration section.

The Applicant is claiming a categorical exclusion from the requirement to prepare an Environmental Assessment based on 21 CFR 25.31(b) and the claim was found acceptable.

The overall information for the Drug Product provided in the initial NDA and subsequent amendments was found acceptable. For further details refer to the Drug Product Review, below.

Labeling: Adequate

As mentioned above, the labeling information was not submitted in the current NDA. Instead, the labeling information, including a revised package insert, which combines four different dosage forms of posaconazole: injection, delayed-release tablet, oral suspension and for delayed-release oral suspension, was submitted in the associated efficacy supplement NDA 205596/S-012. Several revisions have been recommended in the applicable product quality sections (Sections 3, 11 and 16) of the package insert (PI) and in the container label, and carton labeling. These revisions include a correction to the established name for the new dosage form of posaconazole, which should read: posaconazole for delayed-release oral suspension (for details, refer to the Labeling Review, below).

Labeling recommendations have been communicated to OND PM and conveyed to the Applicant. The labeling review and negotiations are currently pending.

Manufacturing: Adequate

Process

(b) (4)

[redacted]

(b) (4)

During the review, additional information was requested by the FDA and submitted to the NDA by the Applicant; that included, for example, a detailed flow diagram (b) (4)

The overall information provided in the initial NDA submission and the subsequent amendments regarding the proposed manufacturing process and controls have been found adequate by the OPMA Reviewer.

Facilities

The drug product facilities include (b) (4), a facility that is used for the manufacture of posaconazole powder (PFS), also used for NDA 205053. This facility is currently compliant with an adequate inspectional history. Merck Sharpe and Dohme, which performs the PFS filling and secondary kit co-packaging site, has an adequate inspectional history and extensive experience in both powder-filling operations and assembling drug/device convenience kits for other approved drug products. In addition, the drug substance manufacturer (b) (4) which is the same facility used for the manufacture of posaconazole drug substance for NDA 205053, was also found to be compliant.

During the facility evaluation, it was determined that the suspension vehicle manufacturing site (Paddock Laboratories LLC) may have elevated risks due to inadequate monitoring of (b) (4) Therefore, a 704(a)(4) document review was performed in lieu of an onsite prior-approval inspection (PAI) to examine the (b) (4) monitoring plan, installation/validation of (b) (4) at the site, analytical testing of the suspension vehicle (including microbial testing), and executed batch records. At the conclusion of the document review, Paddock Laboratories LLC was found to be acceptable to manufacture the suspension vehicle for this drug product.

All manufacturing facilities have been found acceptable by OPMA and are commended for approval (for details refer to the Manufacturing Integrated Assessment, below).

Biopharmaceutics: Adequate

This biopharmaceutics assessment focused on the evaluation on the adequacy of the overall information/data supporting (i) the in vitro dissolution method and acceptance criteria as a quality control (QC) test, (ii) need for bridging between the clinical and to-be-marketed drug products, and (iii) in vitro alcohol dose dumping study.

The originally proposed dissolution method was conducted using the powder with a paddle speed of 75 rpm. The Applicant was recommended to use the constituted suspension, instead of the powder, in the dissolution test since this is the dosage form that will be administered to the patient. In addition, the Applicant was recommended to use a lower paddle speed of 65 rpm based on the limited submitted data from suspension samples. In a teleconference between FDA and the Applicant on March 16, 2021, the Applicant indicated that they could not accumulate adequate data and information to support a revised dissolution method using suspension samples during this NDA review cycle. Instead, the Applicant agreed to revise the dissolution method prior to the commercial launch of the product via a PMC study. As part of this study report, the Applicant also agreed to submit a method validation report and include additional dissolution data for constituted suspension samples from unexpired batches using 65 rpm and 75 rpm to determine an appropriate paddle rotation speed.

The manufacturing site and formulation of powder and suspending vehicle for the drug product used in the pivotal pediatric study P097 are the same as those for the to-be-marketed product. Therefore, no additional bridging is needed.

The results of the in vitro alcohol dose dumping study using the constituted suspension samples in 0.1N HCl containing 0%, 5%, 10%, 20% and 40% alcohol indicated that the in vitro drug release was increased in 0.1N HCl media when the concentration of alcohol was increased. Therefore, the delayed-release characteristics may not be maintained in vivo in the presence of alcohol. This information was conveyed to the Clinical Pharmacology Reviewer for labeling considerations.

For further details refer to the Biopharmaceutics Review, below.

Microbiology: Adequate

The microbiology assessment focused on microbiological quality and controls of the posaconazole powder (PFS), the suspending liquid and the final suspension. During the NDA review several comments and requests for additional data were conveyed to the Applicant.

The manufacturing processes, microbial control methods, and batch sizes have been adequately described for the suspending vehicle. In addition, the results of the Antimicrobial Effectiveness were found acceptable and demonstrate an adequate microbial control at the minimum preservative concentration ((b) (4) % of label claim) through the proposed shelf life of (b) (4) months.

The batch analyses for the suspending vehicle initially did not include results of *Burkholderia cepacia complex* (BCC) testing since the stability batches were manufactured prior to the establishment of BCC testing in USP <60>. However, the firm has committed to conduct the BCC testing on all future batches prior to commercial release. In addition, at the FDA request, the Applicant has provided the results of the method suitability studies to demonstrate that the BCC testing of the suspending vehicle can be performed adequately and accurately as per USP<60>.

The Applicant also provided data to demonstrate that the PFS manufacturing process controls and control of environmental conditions consistently resulted in batches with (b) (4) . Therefore, the exclusion of (b) (4) testing at the batch release was found acceptable. In addition, the risk assessment provided to justify the exclusion of microbial testing in stability studies for posaconazole PFS was also found acceptable (b) (4) .

The stability data submitted in the NDA support the proposed shelf life for both posaconazole PFS and the suspending vehicle from the microbiological quality perspective. In addition, the product quality microbiology information was submitted in the NDA to support the description of the product preparation and administration included in the package insert.

The overall product quality microbiology information submitted in the original NDA submission and subsequent amendments was found adequate. For further details refer to the Microbiology Review, below.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	Formulation Raw materials Process parameters Scale/equipment Site	Low	(b) (4)	Acceptable	
Content uniformity	Formulation Raw materials Process parameters Scale/equipment Site	Low		Acceptable	
Physical stability	Formulation Raw materials Process parameters Scale/equipment Site	Medium		Acceptable	
Microbial limits	Formulation Raw materials Process parameters Scale/equipment Site	Low		Acceptable	
Dissolution	Formulation Raw materials Process parameters Scale/equipment Site	Medium		*Acceptable – further studies pending*	*New dissolution method to be developed via a PMC study*
Dosing accuracy	Formulation Raw materials Process parameters	Medium		*Acceptable – further studies pending*	*New administration method to be developed to be able to administer 10 mL suspension*

Dorota Matecka

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NDA 214770
MEMORANDUM

Application Number: 214770
Product Name: NOXAFIL® (posaconazole) powder for delayed-release oral suspension
Applicant Name: Merck Sharp & Dohme Corp.
Subject: Drug Substance information cross-referenced to NDA 022003

The Applicant cross-references NDA 022003 (posaconazole oral suspension, 40 mg/mL) for drug substance information. The Applicant states that the posaconazole drug substance in NDA 214770 is manufactured through the same process developed and approved for posaconazole oral suspension in NDA 022003, and that no new synthesis was required.

Assessment of the drug substance information in NDA 022003 (and the associated FDA internal review and other cross-referenced NDAs) do not raise concerns, regarding drug substance quality information. The last drug substance supplement for NDA 022003 was Supplement #23 on 12/15/17. The quality information was reviewed and recommend for approval on 03/13/18. No significant drug substance information has been submitted since that review. The cross-referenced information in NDA 022003 is considered adequate to support the approval of NDA 214770.

Rajan Pragani

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Ali Al Hakim

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name Established name(s) Route(s) of administration	(b) (4)	Inadequate (b) (4) Revise to read "(posaconazole) for delayed-release oral suspension"
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4) (b) (4) delayed-release oral suspension 300 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Noxafil oral suspension is not [redacted (b) (4)] with Noxafil delayed-release tablets or Noxafil [redacted (b) (4)] for delayed-release oral suspension due to the differences in the dosing of each formulation. Therefore, follow the specific dosage recommendations for each of the formulations [see Dosage and Administration (2.2, 2.3, 2.8)]. Noxafil [redacted (b) (4)] for delayed-release oral suspension • Administer with [redacted (b) (4)] food [see Clinical Pharmacology (12.3)]. • To ensure delivery of the correct dose, ONLY the provided notched tip syringes must be used for preparation and administration. The design of the notched tip syringe prevents aggregation of the suspension during preparation and administration [see Dosage and Administration (2.7)].	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	(b) (4)	Inadequate
Strength(s) in metric system		(b) (4)
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	NA	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	See above	See above
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	See List names of all inactive ingredients.	Adequate
Dosage form(s) and route(s) of administration		
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	NA	NA
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	(b) (4)	Inadequate: Revise to ensure all items are in alphabetical order. We recommend revision to, "Noxafil for delayed-release oral suspension is supplied as a component of a kit. Each kit contains Noxafil as an off-white to yellowish powder for delayed-release oral suspension, a bottle of mixing liquid, two 3 mL (green) notched tip syringes, two 10 mL (blue) notched tip syringes, two mixing cups, and one bottle adapter for the mixing liquid bottle…."
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA

Statement of being sterile (if applicable)	NA	NA
Pharmacological/ therapeutic class	(b) (4)	Inadequate Revise to "Noxafil (posaconazole)…."
Chemical name, structural formula, molecular weight	Posaconazole is designated chemically as 4-[4-[4-[4-[[(3R,5R)-5-(2,4-difluorophenyl)tetrahydro-5- (1H-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1S,2S)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one with an empirical formula of C37H42F2N8O4 and a molecular weight of 700.8. The chemical structure is:	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Posaconazole is a white powder with a low aqueous solubility.	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA

Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”	NA	NA

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) Strength(s) in metric system Available units (e.g., bottles of 100 tablets) Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4) for Delayed-Release Oral Suspension Noxafil (b) (4) for Delayed-Release Oral Suspension is supplied as: Package A: a kit with 8 child-resistant single-use packets of Noxafil (b) (4) for Delayed-Release Oral Suspension 300 mg, two 3 mL (green) notched tip syringes, two 10 mL (blue) notched tip syringes, two mixing cups, one mixing liquid bottle, and one bottle adapter for the mixing liquid bottle. Package B: a box of six 3 mL (green) and six 10 mL (blue) notched tip syringes. NDC 0085-2224-02 unit of use carton with 8 packets. NDC 0085-2224-01 individual packet. (b) (4)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	(b) (4)	Inadequate Revise to "Store the entire kit at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F) in a clean, dry place. Do not open foil packet containing Noxafil for delayed-release oral suspension until ready for use. Storage conditions for the reconstituted solution are presented in another section of the prescribing information *[see Dosage and Administration (2.7)]."*
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	NA	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	See above section on special handling	Inadequate Replace "-" with "to" to avoid confusion with minus sign
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	NA
Include information about child-resistant packaging	Package A: a kit with 8 child-resistant single-use packets of Noxafil (b) (4) for Delayed-Release Oral Suspension 300 mg, two 3 mL (green) notched tip syringes, two 10 mL (blue)	Adequate Applicant confirmed the commercial packaging is compliant with 16 CFR 1700 (child resistant).

	notched tip syringes, two mixing cups, one mixing liquid bottle, and one bottle adapter for the mixing liquid bottle. Package B: a box of six 3 mL (green) and six 10 mL (blue) notched tip syringes. NDC 0085-2224-02 unit of use carton with 8 packets.	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of MERCK & CO., INC., Whitehouse Station, NJ 08889, USA	Adequate

2.0 PATIENT LABELING

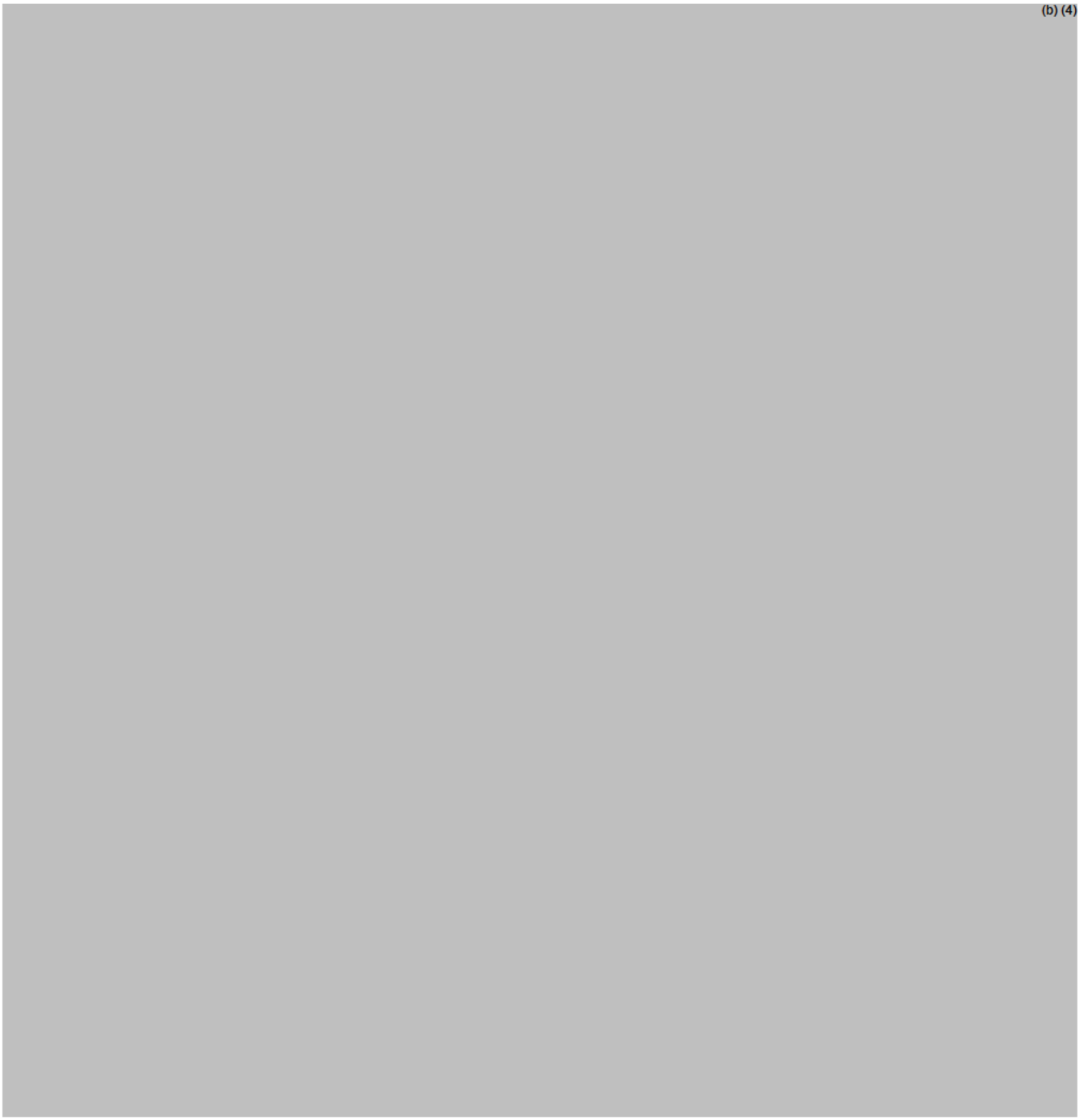
Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)



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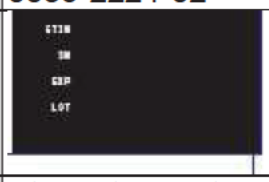
Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	(b) (4)	Inadequate (b) (4) (b) (4) Revise to read "(posaconazole) for delayed-release oral suspension"
Dosage strength	300 mg	Adequate
Route of administration	For oral administration	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	Adequate
Net contents (e.g. tablet count)	8 packets	Adequate
"Rx only" displayed on the principal display	Rx only	Adequate
NDC number	0085-2224-02	Adequate
Lot number and expiration date		Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at room temperature between 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (59°F to 86°F). Store in the original container. Do not open foil packet(s) until ready for use.	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code		Adequate

Item	Information Provided in the NDA	Assessor’s Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: Merck Sharp and Dohme Corp., a subsidiary of Merck &Co., Inc.	Adequate
Medication Guide (if applicable)	See below	Adequate
No text on Ferrule and Cap overseal	NA	NA
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	NA
And others, if space is available	NA	NA

Assessment of Carton and Container Labeling: *Adequate*

The only proposed revision is that the container label for the suspending vehicle be revised to list the excipients in alphabetical order. However, this is minor. Overall,

there are no issues from a CMC perspective regarding the carton and container labeling.
Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Adequate, pending the Applicant's acceptance of the revisions noted above in red. It should be noted that during the course of review, an Information Request for videos of alternative mixing methods was requested. The Applicant responded (eCTD 0021) that videos were not made as the proposed drug product is to only be mixed according to the IFU and no other sample preparation is recommended. This is acceptable.

Overall Assessment and Recommendation:

This application is recommended for approval per labeling/labels perspective once the following changes have been made to the label.

Grace Chiou

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Thomas Oliver

Digitally signed by Thomas Oliver
Date: 5/20/2021 09:43:25AM
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BIOPHARMACEUTICS

NDA: 214770 [505(b)(1)]
Drug Product Name/Strength: NOXAFIL® (posaconazole) for Delayed-Release oral suspension, 300 mg
Route of Administration: Oral
Proposed Indication: Prophylaxis and salvage treatment of invasive fungal infections (IFI) in children and adolescents (aged 2 to <18 years)
Applicant Name: Merck Sharp & Dohme Corporation (Merck & Co., Inc)
Submission Date: 07/31/2020
Primary Reviewer: Kevin Wei, Ph.D.
Secondary Reviewer: Elsbeth G Chikhale, Ph.D.
Recommendation: Approval with PMC

EXECUTIVE SUMMARY

Merck & Co., Inc. submitted this NDA 214770 for Posaconazole (POS) for delayed-release (DR) oral suspension as a new oral powder for suspension formulation indicated for prophylaxis and salvage treatment of invasive fungal infections (IFI) in children and adolescents (aged 2 to <18 years). (b) (4) The proposed drug product is a powder for suspension, co-packaged with the suspending vehicle and a syringe.

The Applicant submitted this NDA in conjunction with an efficacy supplement NDA (sNDA) 205596 (S-12, IV injection) which containing the clinical and labeling information to support the NOXAFIL® pediatric indication. In addition, the Applicant cross-referenced their approved products: POS Oral Suspension (NDA 022003) and POS DR Tablets (NDA 205053) for information regarding the drug substance and drug product, respectively.

This Biopharmaceutics review focused on the evaluation on the adequacy of the overall information/data supporting (i) the in vitro dissolution method and acceptance criteria as a quality control (QC) test, (ii) need for bridging between the clinical and To-Be-Marketed (TBM) drug products, and (iii) in vitro alcohol dose dumping study.

In vitro dissolution method and acceptance criteria:
POS is a low solubility drug substance as per BCS criteria. The Applicant proposed a two-stage dissolution method consisted of acid and buffer stages as follows:

Dissolution Sample	POS powder (content of one sachet)
USP Apparatus	II (Paddle)
Rotation Speed	75 rpm
Temperature:	37 °C ± 0.5 °C

Medium	Acid stage: 0.01 N HCl; Buffer stage: pH 6.8 Phosphate buffer with 1.3% Tween 80;
Volume	Acid stage for 120 minutes: 750 mL; Buffer stage: 1000 mL (after 120 minutes, while stirring, add about 250 mL of 0.2 M phosphate buffer solution with appropriate concentrations of Tween 80 for a final concentration of 1.3% Tween 80)

The originally proposed dissolution method was conducted using the POS powder with a paddle speed of 75 rpm. The Applicant was recommended to use the POS constituted suspension, instead of POS powder, in the dissolution test to reflect the administrative dosage form to the patient. In addition, the Applicant was recommended to use a lower paddle speed of 65 rpm based on the limited submitted data from suspension samples. In a teleconference between FDA and the Applicant on 03/16/2021, the Applicant indicated that they could not accumulate adequate data and information to support a revised dissolution method using suspension samples during the course of the NDA review due to the limited available unexpired batches and the lack of sufficient time for method development and validation. Instead, the Applicant agreed to a post marketing commitment (PMC) (see Biopharmaceutics IR response dated 03/31/2021 (0023(23)[1]) to submit the following report and data by 08/31/2021 (3 months after the PDUFA date of 05/31/2021), prior to the commercial launch of the product, for FDA's review and concurrence of the revised dissolution method and acceptance criterion/criteria:

- A dissolution method validation report for a revised dissolution method using the constituted suspension samples.
- Additional dissolution data for suspension samples from additional unexpired batches using 65 rpm and 75 rpm to determine an appropriate paddle rotation speed.

Bridging:
In the co-submitted sNDA 205596 (S-12, IV injection), the Applicant conducted one pivotal pediatric study P097 to support expansion of the currently approved adult indications to the pediatric population based on a bridging approach between the POS for DR suspension formulation and the intravenous (IV) formulation. The manufacturing site and formulation of powder and suspending vehicle for POS for DR suspension used in the pivotal pediatric study P097 are the same as those for the To-Be-Market (TBM) product. Thus, no additional bridging is needed.

In vitro alcohol dose dumping study:
The Applicant was requested to submit an in vitro alcohol dose dumping study using the constituted suspension samples in 0.1N HCl containing 0%, 5%, 10%, 20% and 40% alcohol. The submitted data indicate that in vitro drug release was increased in 0.1N HCl media when the concentration of alcohol was increased. Therefore, the delayed-release characteristics may not be maintained in vivo in the presence of alcohol. This information

[1] \\CDSESUB1\evsprod\nda214770\0023\m1\us\quality-information-amendment-31mar2021.pdf

was conveyed to the Clinical Pharmacology Reviewer, for consideration in the label or need to request additional in vivo information.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 214770 for NOXAFIL® (posaconazole) delayed-release oral suspension, 300 mg, is recommended for **APPROVAL with a Post-Marketing Commitment [PMC].** The Applicant agreed to a PMC to submit a dissolution method validation report for a revised dissolution method using the constituted suspension samples and additional dissolution data for suspension samples from additional unexpired batches using 65 rpm and 75 rpm to determine an appropriate paddle rotation speed by 08/31/2021, prior to the commercial launch of the drug product.

Note:
A final decision for this NDA has not been made by the Clinical team at the end of the current Biopharmaceutics review cycle. The final language for the management cleared, agreed upon PMC will be documented in an addendum to this review if the NDA is approved by the PDUFA date of 05/31/2021. If a Complete Response (CR) action is recommended for this NDA, this language will be conveyed to the Applicant in the CR letter. If the review clock is extended and the Applicant submits additional dissolution data and information within the extended review cycle, an addendum to this review will be conducted if sufficient review time is allowed.

BIOPHARMACEUTICS REVIEW

1. Drug Substance (DS) solubility and permeability

The Applicant cross-referenced their marketed products, Oral Suspension, 40 mg/mL (NDA 022003) for information for the DS. The submitted solubility of (b) (4) POS DS showed that POS has low solubility (< 0.001 mg/mL) in aqueous media with pH > 3 and is relatively soluble (~0.8 mg/mL) in 0.1N HCl.

(b) (4)

The Applicant claimed that POS is a lipophilic compound with high permeability[2]. The submitted Caco-2 study showed that in-vitro permeability was higher than 10^{-5} cm/s. However, the Applicant's submitted mass balance study (b) (4) showed that drug-derived radioactivity for POS was recovered predominantly in the feces (77%) with lesser amounts in the urine (14%). The Applicant determined that the absolute bioavailability (BA) for DR Tablets is approximately 50% (Study P07783, NDA 205053) in adults and is approximately 70-80% (Study P097, NDA 205596/S-12) for DR oral suspension.

Reviewer's Assessment:

The submitted data indicated that POS is a low solubility DS as per BCS criteria. It's noted that (b) (4) *. The submitted in vitro Caco-2 study data (Papp of 3.4 x 10-5 cm/sec) indicated that POS is a high permeability DS, but these findings are not supported by the in vivo studies (e.g., absolute BA and mass balance).*

2. To-Be-Market (TBM) product

The proposed POS for DR oral suspension (kit) is comprised of the sachets (powder), co-packaged suspending vehicle (9 ml), notch-tip oral dosing syringes, press in bottle adaptor (PIBA) and mixing cups. The sachets contain (b) (4) powder mixture of 300 mg POS and (b) (4) HPMCAS (b) (4) Prior to dosing, the POS powder is dispersed in 9 mL of suspending vehicle to obtain the DR oral suspension

[2] \\CDSESUB1\evsprod\nda205053\0000\m2\23-qos\drug-product.pdf

with a final concentration of approximately 30 mg/mL. The compositions of POS powder (in sachet) and co-packaged suspending vehicle are shown as below:

Table 2. Composition of POS powder (sachet)
(*3.2.P.1 Finished Product Composition*, Table 1, Page 1)

Component	Reference to Quality Standard	Function	Amount per Sachet (mg)	Amount per Sachet (%w/w)
Posaconazole	In-house Standard	Drug Substance	300.0	(b) (4)
Hypromellose acetate succinate, (b) (4)	USP-NF	(b) (4)	(b) (4	
Theoretical Dose Weight of Posaconazole Powder for Oral Suspension				100.0

Table 3. Composition of suspending vehicle (9 mL)
(*3.2.P.2 Pharmaceutical Development/Drug Product*, Table 5, Page 6)

Ingredient	Compendial Status	Function	%	Weight / bottle (g)
Purified Water	USP			(b) (4)
Glycerin	USP/ Ph. Eur.			
Methylparaben	NF/ Ph. Eur.			
Propylparaben	NF/ Ph. Eur.			
Sodium Phosphate Monobasic Monohydrate	USP			
Citric Acid, Anhydrous	USP/ Ph. Eur.			
Xanthan Gum	NF/ Ph. Eur.			
Sodium Citrate	USP/ Ph. Eur.			
Sodium Saccharin	USP/ Ph. Eur.			
Microcrystalline Cellulose & Carboxymethyl Cellulose	NF/ Ph. Eur.			
Carrageenan Calcium Sulfate Trisodium Phosphate	In-house			
Sorbitol Solution	USP			
Potassium Sorbate	NF/ Ph. Eur.			
Flavor Berry Citrus Sweet PF	In-house			
Antifoam Af Emulsion	In-house			

3. Dissolution method development

(b) (4)

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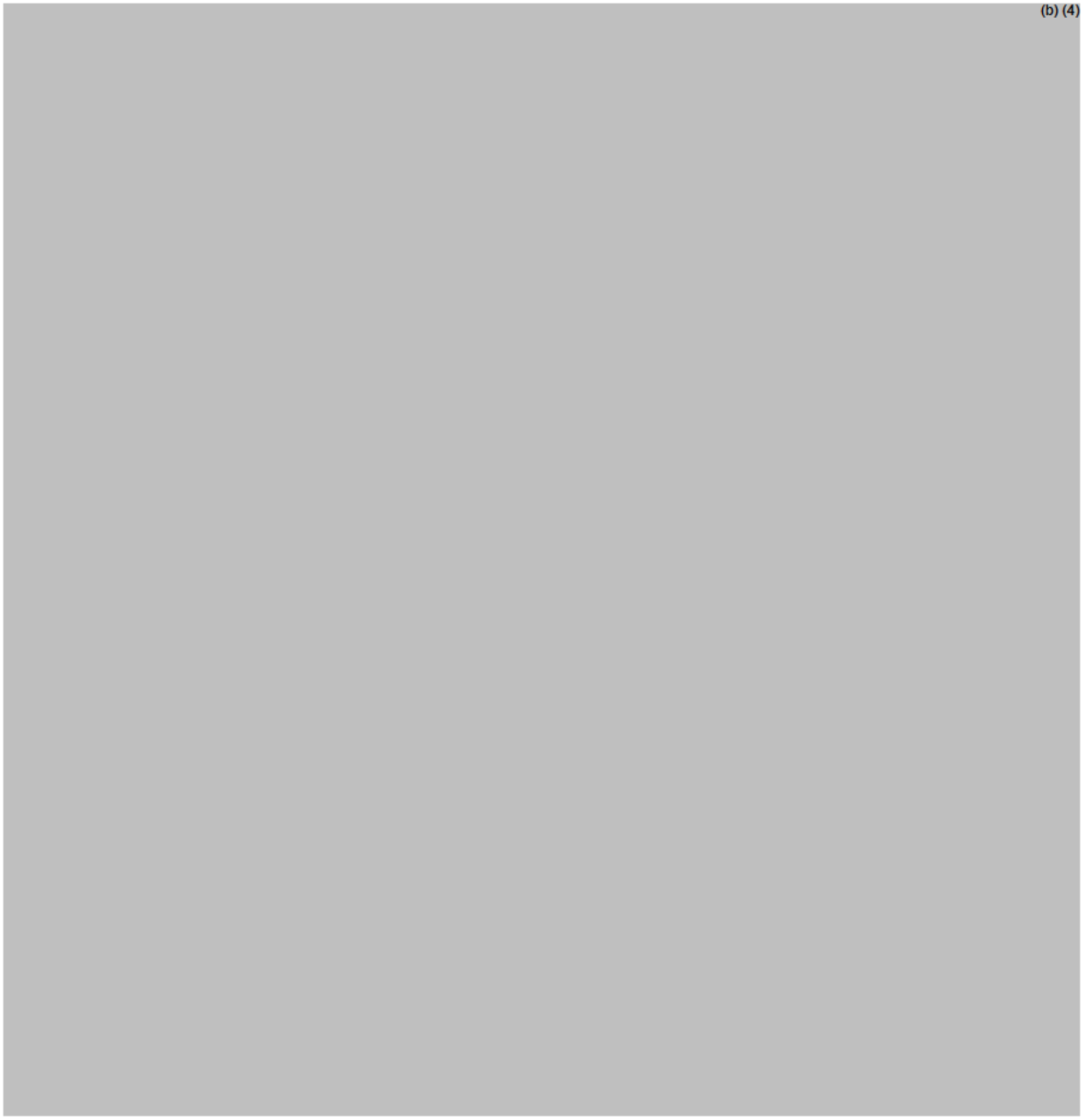
(b) (4)



3.5 Analytical procedures and method validation

The Applicant submitted the dissolution analytical procedure and method validation in Module 3.2.P.5.2. and 3.2.P.5.3., respectively.

Reviewer's Assessment/Note:
See above section 3.1. According to Module 3.2.P.5.2 Analytical Procedures (Section B, Page 1), the entire content of one sachet was added into the test vessel during the sample preparation. The Applicant was requested to revise the sample preparation and use the constituted suspension samples in the dissolution test (Biopharmaceutics IR dated 03/04/2021). As per T-con discussion between FDA and the Applicant dated 03/16/2021, the Applicant stated that they did not have sufficient time to validate a revised dissolution

method using the suspension samples during the course of the NDA review and agreed to a post marketing commitment (PMC) (see Biopharmaceutics IR response dated 03/31/2021 (0023(23)) to submit a dissolution method validation report for a revised dissolution method using the constituted suspension samples by 08/31/2021 for FDA's review and concurrence of the new dissolution method. The HPLC method validation for specificity, linearity and range, accuracy, precision, solution stability and robustness will be reviewed by the drug product reviewer.

4. Dissolution acceptance criteria

The Applicant proposed the acceptance criteria for the two-stage dissolution method as NMT (b) (4)% at 120 minutes for acid stage and Q (b) (4)% at 145 minutes at buffer stage.

Reviewer's Assessment/Note:
See above section 3.1. As per T-con discussion between FDA and the Applicant dated 03/16/2021, the Applicant could not accumulate adequate data and information to support the recommended dissolution conditions using the constituted suspension samples during the course of the NDA review. The Applicant agreed to a post marketing commitment (PMC) (see Biopharmaceutics IR response dated 03/31/2021 (0023(23)) and committed to submit additional dissolution data for suspension samples from additional unexpired batches using 65 rpm and 75 rpm to determine an appropriate paddle rotation speed by 08/31/2021 for FDA's review and concurrence of the new dissolution method and acceptance criteria, prior to the commercial launch of the product. The current dissolution method and acceptance criterion is accepted on an interim bases if the NDA is approved, however, will not be used prior to launch of any commercial batches (per PMC).

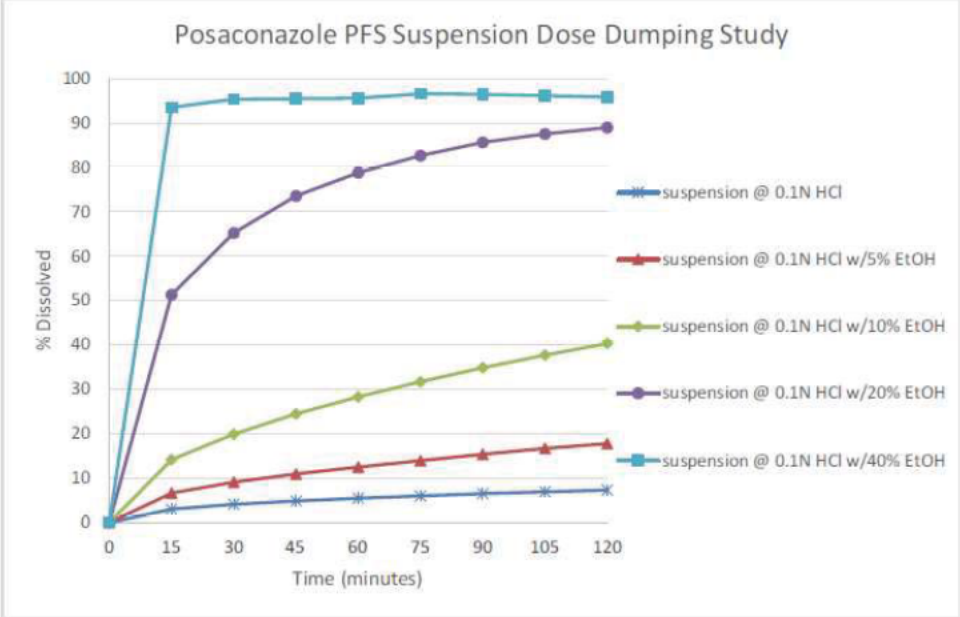
5. In vitro alcohol dose dumping study

In the NDA submission, the Applicant claimed that "the pediatric patients are not expected to ingest alcohol", so the impact of alcohol dose dumping potential was not evaluated (*3.2.P.2, pharmaceutical Development/Drug Product, Page 12*).

Reviewer's Assessment:
The package inserts in NDA 214770 and NDA 205596 (S-012) do not contain a caveat to refrain from alcoholic consumption with the proposed product. Although the POS for DR suspension is proposed for the pediatric patients, but it does not exclude the other patient population in the labeling claims (e.g., geriatric patients, patients with swallowing disorders etc.) who may use alcohol. Therefore, the Applicant was requested to submit an in vitro alcohol dose dumping study using the constituted suspension samples at 65 rpm in 0.1N HCl dissolution media containing 0%, 5%, 10%, 20% and 40% alcohol to determine if the delayed release characteristics are maintained in the presence of alcohol (Biopharmaceutics IR dated 03/04/2021/T-con dated 03/16/2021).

Applicant's IR response dated 04/02/2021 (0025(24)):
The Applicant submitted the in-vitro alcohol dose dumping study using the suspension samples (constituted with the suspending vehicle) for Lot 0000823965 with a paddle speed of 65 rpm in 0.1N HCl dissolution media containing 0%, 5%, 10%, 20% and 40% alcohol, respectively.

Figure 12. Dissolution profiles of suspension samples in 0.1N HCl containing alcohol (*Module 1.11.1 (0025), Figure 1, Page 3*)



Reviewer's Assessment:
The submitted data indicate that in vitro drug release was increased in 0.1N HCl media when the concentration of alcohol was increased, as shown in the above Figure 12. Therefore, the delayed-release characteristics of the POS for DR suspension may not be maintained in vivo in the presence of alcohol. The Office of Clinical Pharmacology (OCP) was notified and OCP will determine if this can be addressed in labeling (e.g. do not consume alcohol while on this medication or similar language) or by requesting an in vivo drug product-alcohol interaction study.

6. Bridging

The Applicant co-submitted an efficacy sNDA 205596 (S-12, IV injection) to support expansion of currently approved adult indications for prophylaxis and salvage treatment of invasive fungal infections to the pediatric population. The Applicant conducted a pivotal Phase 1B Study P097 (*A Study of the Safety, Tolerability, and Pharmacokinetics of Intravenous (IV) and Powder for Oral Suspension Formulations of Posaconazole (POS) in Immunocompromised Pediatric Subjects with Neutropenia*) to bridge the POS for DR oral suspension to the IV formulation. The PK parameters following the administration of TBM DR oral suspension and IV formulation in immunocompromised pediatric subjects aged 2 to 17 years were summarized as below.

Table 12. PK parameters comparison following multiple dose POS IV and DR oral suspension administration in immunocompromised pediatric subjects
(*NDA 205596 (S-12), Module 5.3.3.2/P097MK5592,* Table 11-1, Page 66)

Dose Cohort	Age Group	Dose Type	N	Cmax (ng/mL)[1]	Tmax (hr)[2]	AUC0-24 (hr*ng/mL)[1]	C0 (ng/mL)[1]	Cmin (ng/mL)[1]	Cavg (ng/mL)[1]	CL (L/hr)[1]	CL/F (L/hr)[1]
1: 3.5 mg/kg[3,6,7,22]	1 (2 to <7 yrs old)	IV	11	1590 (43.1)	1.78 (1.67 - 5.53)	17800 (55.0)	424 (82.4)	400 (81.3)	743 (55.0)	3.39 (52.8)	---
		PFS	5	884 (44.4)	3.83 (1.92 - 4.25)	12200 (36.0)	261 (40.7)	254 (45.6)	510 (36.0)	---	4.97 (29.1)
	2 (7 to 17 yrs old)	IV	19	2450 (72.7)	1.77 (0.00 - 3.50)	27300 (49.7)	802 (90.4)	670 (65.1)	1140 (49.7)	6.64 (38.6)	---
		PFS	10	1340 (30.8)	2.20 (1.92 - 8.05)	20700 (33.8)	629 (46.5)	579 (44.9)	861 (33.8)	---	7.67 (39.9)
2: 4.5 mg/kg[3,6,7,22]	1 (2 to <7 yrs old)	IV	14	2320 (39.8)	1.78 (1.42 - 5.90)	25600 (30.0)	542 (60.2)	501 (56.8)	1070 (30.0)	2.97 (36.2)	---
		PFS	8	1550 (40.8)	3.82 (1.88 - 5.92)	21600 (64.5)	616 (151.9)	476 (164.6)	901 (64.5)	---	3.49 (59.1)
	2 (7 to 17 yrs old)	IV	15	2310 (40.3)	1.75 (1.52 - 1.80)	29800 (42.9)	824 (62.8)	737 (66.0)	1240 (42.9)	6.69 (37.3)	---
		PFS	8	1670 (28.5)	6.14 (1.98 - 7.98)	28700 (33.7)	827 (54.3)	790 (48.2)	1200 (33.7)	---	7.84 (49.4)
3: 6.0 mg/kg[3,6,7,11,22]	1 (2 to <7 yrs old)	IV	17	3060 (54.1)	1.75 (1.57 - 1.83)	31100 (48.9)	697 (98.2)	626 (104.8)	1300 (48.9)	3.27 (49.3)	---
		PFS	7	1510 (43.4)	4.00 (2.17 – 7.92)	23000 (47.3)	593 (82.8)	542 (68.8)	960 (47.3)	---	4.60 (35.2)
	2 (7 to 17 yrs old)	IV	24	3340 (39.4)	1.77 (1.33 - 6.00)	44200 (41.5)	1290 (53.5)	1160 (60.4)	1840 (41.5)	4.76 (55.7)	---
		PFS	12	1370 (178.5)	2.78 (0.00 - 4.00)	25000 (184.3)	902 (141.8)	713 (300.6)	1040 (184.3)	---	8.39 (190.2)

[1]Geometric mean (%GCV); [2]Median (Min - Max).
[3]24hr sample was drawn after next day dose, hence, predose concentrations were imputed for 24hr for 1 subject in the following groups: AG1 DC2 IV, AG2 DC1 IV & AG1 DC3 IV and 2 subjects in the following groups: AG1 DC3 PFS & AG2 DC3 IV.
[6]Missing C24hr values were imputed with predose concentrations for the 1 subject in AG1 DC2 PFS, 2 subjects in AG1 DC1 PFS & AG1 DC3 PFS and 5 subjects in AG2 DC3 PFS
[7]AUC0-last was reported in place of AUC0-24hr in cases where the actual time of C24hr was less than 24hr and AUC0-24 is unable to be calculated; this applies to 1 subject in AG2 DC1 PFS, 1 subject in AG1 DC2 IV, 1 subject in AG1 DC2, PFS, 4 subjects in AG2 DC2 PFS, 1 subject in AG1 DC3 PFS, 1 subject in AG2 DC3 IV, 1 subject in AG2 DC3 PFS.
[11]AN (b) (6) predose concentration was 0. Hence, C24hr sample was imputed for predose.
[22]AN (b) (6) AG2 DC3 IV) had very high concentration values. Hence, considered as outlier subject in this group and excluded from the analysis.
[3]Clearance (CL for IV and CL/F for PFS) was calculated using AUC0-last was imputed for AUC0- tau in cases where AUC0-tau is unable to be calculated: this applies to 1 subject in AG2 DC1 PFS, 1 subject in AG1 DC2 IV, 1 subject in AG1 DC2, PFS, 4 subjects in AG2 DC2 PFS, 1 subject in AG1 DC3 PFS, 1 subject in AG2 DC3 IV, 1 subject in AG2 DC3 PFS.

Reviewer's Assessment:

The PK parameters will be reviewed by the Clinical Pharmacology reviewer and the safety and tolerability will be reviewed by the Clinical reviewer. Because the composition and manufacturing process/site (Module 3.2.P.3.1) for the POS powder and suspending vehicle used in the pivotal pediatric study P097 are the same as that for the proposed TBM products, no additional bridging is needed.

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Elsbeth Chikhale

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	214770
Assessment Cycle Number	01
Drug Product Name/ Strength	Posaconazole (Noxafil) / 300 mg
Route of Administration	Oral suspension
Applicant Name	Merck Sharp & Dohme Corp.
Therapeutic Classification/ OND Division	CDER/OND/OID/DAI
Manufacturing Site	(b) (4)
Method of Sterilization	N/A - Non-sterile product

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD seq #0001	07/31/2020
eCTD seq #0005	10/27/2020
NDA 205596, seq #0090	07/31/2020
eCTD seq #0010	12/21/2020
eCTD seq #0013	01/29/2021
eCTD seq #0020	03/08/2021
eCTD seq #0022	03/17/2021

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The drug product is a new age-appropriate oral formulation for Posaconazole (Noxafil) in the form of delayed-release oral powder for suspension (PFS) indicated for prophylactic treatment of invasive fungal infections in pediatric patients. The labeling information is cross-referenced in an efficacy supplement NDA 205596/S-012. The review includes information requests sent on 10/09/2020, 12/08/2020, 01/15/2020, and 03/12/2021 as well as responses received on 10/27/2020, 12/21/2020, 01/29/2021, 03/08/2021, and 03/17/2021.

Concise Description of Outstanding Issues: None

Supporting Documents: None

S DRUG SUBSTANCE

The manufacturing process for the drug substance is not reviewed because the drug product is non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

PFS section 3.2.P.1, pg. 1-3/3 in "description-and-composition.pdf"

The drug product is a kit with a carton containing the following items:

- Eight sachets of Posaconazole powder for oral suspension (PFS)
- One bottle of Suspending Vehicle
- Two mixing cups
- Two 3 mL green notch-tip oral dosing syringes
- Two 10 mL blue notch-tip oral dosing syringes
- One press-in bottle adapter (PIBA)
- Literature
- A syringe pack with six 3mL and six 10 mL notch-tip oral dosing syringes

Posaconazole PFS: Each single-use sachet contains (b) (4) Posaconazole (active drug substance) and (b) (4) Hypromellose acetate succinate (b) (4) both in powder form (b) (4)) and packaged in a child-resistant foil laminate sachet (b) ( ) *PFS section 3.2.P.7, pg. 3-4/25 in "container-closure-system.pdf"*).

`Suspending vehicle (b) (4) The suspending vehicle is (b) (4) packaged in 16 oz (473 mL) white HDPE bottle with (b) (4) closure (Vehicle section 3.2.P.7, pg. 2/11 in "container-closure-system.pdf"). (b) (4) he composition of the suspending vehicle is listed below (Vehicle section 3.2.P.1, pg. 1/1 in "description-and-composition.pdf"):

Ingredient	Compendial Status	Function	%	Weight / bottle (g)
Purified Water	USP	(b) (4)		
Glycerin	USP/ Ph. Eur.			
Methylparaben	NF/ Ph. Eur.			
Propylparaben	NF/ Ph. Eur.			
Sodium Phosphate Monobasic Monohydrate	USP			
Citric Acid, Anhydrous	USP/ Ph. Eur.			
Xanthan Gum	NF/ Ph. Eur.			
Sodium Citrate	USP/ Ph. Eur.			
Sodium Saccharin	USP/ Ph. Eur.			
Microcrystalline Cellulose & Carboxymethyl Cellulose	NF/ Ph. Eur.			
Carrageenan Calcium Sulfate Trisodium Phosphate	In-house			
Sorbitol Solution	USP			
Potassium Sorbate	NF/ Ph. Eur.			
Flavor Berry Citrus Sweet PF	In-house			
Antifoam Af Emulsion	In-house			

Assessment: ***Adequate***
The drug product compositions and container-closure systems were adequately described.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)

Response received on 10/27/2020

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