CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214770Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 27, 2021
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214770 and NDA 205596/S-012
Product Name and Strength:	Noxafil PowderMix (posaconazole) for delayed-release oral suspension, 300 mg
Applicant/Sponsor Name:	Merck, Sharpe and Dohme Corp.
OSE RCM #:	2020-1604-1
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader (Acting):	Ebony Whaley, PharmD, BCPPS
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, carton labeling, Instructions for Use (IFU) and Patient Information received on May 19, 2021 and May 26, 2021 for Noxafil PowderMix. The Division of Anti-Infectives (DAI) requested that we review the revised labels and labeling for Noxafil PowderMix (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] We note that the Applicant also incorporated revisions that were recommended by the Division of Medical Policy Programs (DMPP)/Patient Labeling Team for the IFU and Patient Information documents.[b]

[a] Johnson, C. Label and Labeling Review for Noxafil PowderMix (NDA 214770 and NDA 205596/S-012). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 12. RCM No.: 2021-787, 2020-1604, 2020-1654.

[b] Jackson, K. Patient Labeling Review for Noxafil PowderMix. Silver Spring (MD): FDA, CDER, OMP, OMPI, DMPP; 2021 MAY 17. NDA214770 and NDA 205596/S-12.

2 DISCUSSION

We note the Applicant implemented all our container label and carton labeling recommendations. We also note the Applicant implemented the majority of our IFU recommendations. However, we note the Applicant proposes an alternative revision to our recommendation to revise IFU Step 12 to include an image depicting an air gap at the tip of the syringe and to include an arrow pointing to the top of the syringe so that users are aware of where to look for air gaps. In their response, the Applicant altered the existing image of the syringe included in IFU Step 12 by including an enlarged view of the air gap at the tip of the syringe and dotted lines pointing to the top of the syringe. We find the Applicant's alternative proposal acceptable from a medication error perspective as this image shows the user where to look for air gaps in the syringe.

3 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 17, 2021
To:	Christopher Smith, PharmD, MPH, BCPS, RAC Regulatory Project Manager **Division of Anti-Infectives (DAI)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Nyedra Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** James Dvorsky, PharmD Team Leader **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name), Dosage Form and Route, Application Type/Number:	Noxafil (posaconazole) for delayed-release oral suspension, NDA 214770 Noxafil (posaconazole) delayed-release tablets, for oral use, NDA 205053 S-12 Noxafil (posaconazole) injection, for intravenous use NDA 205596 S-12
Applicant:	Merck Sharp & Dohme Corp.

1 INTRODUCTION

On July 31, 2020, Merck Sharp & Dohme Corp. submitted for the Agency's review an original New Drug Application (NDA) for Noxafil (posaconazole) for delayed-release oral suspension. This NDA 214770 is submitted in conjunction with the efficacy supplement (sNDA) 205596 to support the Noxafil (posaconazole) pediatric indication for prophylaxis of invasive Aspergillus and Candida infections in patients who are at high risk of developing these infections due to being severely immunocompromised. There is a single Prescribing Information (PI) and Patient Package Insert (PPI) for the delayed-release oral suspension, oral suspension, delayed-release tablets and injection formulations.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anti-Infectives (DAI) on April 15, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for Noxafil (posaconazole) for delayed-release oral suspension, delayed-release tablets, and injection.

MATERIAL REVIEWED

- Draft Noxafil (posaconazole) for delayed-release oral suspension, delayed-release tablets, and injection PPI and IFU received on November 18, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 15, 2021.
- Draft Noxafil (posaconazole) for delayed-release oral suspension, delayed-release tablets, and injection Prescribing Information (PI) received on November 18, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 15, 2021.

2 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU is consistent with the approved comparator labeling where applicable.

3 CONCLUSIONS

The PPI and IFU is acceptable with our recommended changes.

4 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KELLY D JACKSON
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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 12, 2021
Requesting Office or Division:	Division of Anti-Infective Products (DAI)
Application Type and Number:	NDA 214770 and NDA 205596/S-012 and NDA 205596/S-013
Product Type:	Single Ingredient, Co-packaged Combination Product
Drug Constituent Name and Strength	Noxafil PowderMix (posaconazole) for delayed-release oral suspension, 300 mg Noxafil (posaconazole) injection, 300 mg per vial Noxafil (posaconazole) delayed-release tablets, 100 mg Noxafil (posaconazole) oral suspension, 40 mg/mL
Device Constituent:	oral dosing syringe
Rx or OTC:	RX
Applicant/Sponsor Name:	Merck, Sharpe and Dohme Corp., (Merck)
Submission Date:	7/31/2020; 8/19/2020; 10/29/2020; 12/14/2020; 2/12/2021 3/12/2021; 4/22/2021; 4/30/2021
OSE RCM #:	2020-1604 and 2020-1654 and 2021-787
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader (Acting):	Ebony Whaley, PharmD, BCPPS
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA Division Director:	Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

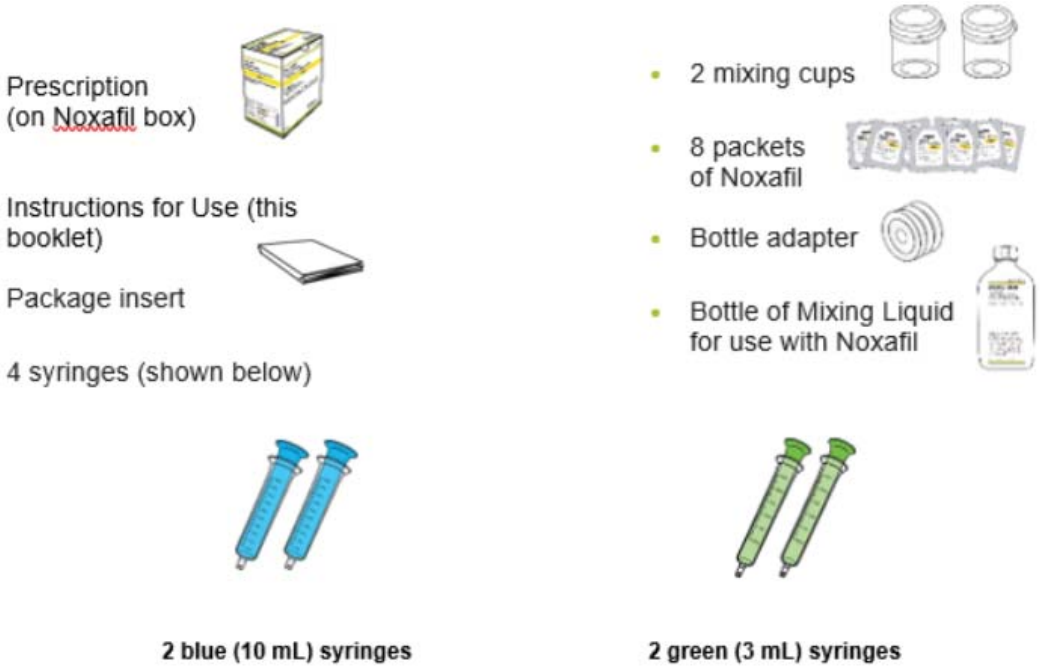
The Division of Anti-Infective Products (DAI) currently has a new application (NDA 214770) as well as two open supplements (NDA 205596/S-012 and NDA 205596/S-013) that they would like to take action on simultaneously. These three actions are related to each other since they are based on newly submitted data and information related to the use of products within the Noxafil product line in a pediatric population. DMEPA was consulted to review the human factors (HF) validation study report and labels and labeling submitted under NDA 214770 and NDA 205596/S-012 for a new dosage form, Noxafil PowderMix for delayed-release oral suspension, 300 mg. The Noxafil PowderMix is a combination product with a proposed oral dosing syringe device constituent part that is intended for the prophylaxis of invasive Aspergillus and Candida infections in patients 2 to less than 18 years of age who are at high risk of developing these infections due to being severely immunocompromised. Furthermore, as part of NDA 205596/S-012, Merck is seeking to add this same pediatric indication for the currently marketed delayed-release tablet and injection formulations.

We also reviewed the revised Prescribing Information (PI) submitted as a part of a prior approval supplement (PAS) under NDA 205596/S-013 for Noxafil (posaconazole) injection to determine whether there are areas of vulnerability that may lead to medication errors. Supplement 13 proposes to expand the indications of Noxafil injection and Noxafil delayed-release tablets to the treatment of invasive aspergillosis (IA) in patients greater than or equal to 13 years of age.

1.1 PRODUCT DESCRIPTION

Noxafil (posaconazole) is currently approved as a 300 mg/vial injection, 100 mg delayed-release tablet, and a 40 mg/mL oral suspension. The newly proposed dosage form, Noxafil PowderMix (posaconazole) for delayed-release oral suspension, is presented as a combination product consisting of a carton (Package A) containing eight sachets of posaconazole powder, one bottle of mixing liquid, two mixing cups, one press-in bottle adapter (PIBA), four oral dosing syringes with custom notch-tips (2 x 10 mL blue syringes and 2 x 3 mL green syringes) (See Figure 1 below). Merck is also proposing an additional carton (Package B) containing 6 x 3 mL and 6 x 10 mL additional syringes that is supplied separately.

Figure 1. Graphic of Posaconazole for delayed-release oral suspension kit contents for Package A



1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On July 31, 2020, Merck submitted an efficacy supplement (S-012) to NDA 205596, to fulfill Postmarket Requirements (PMRs 2090-1 [NDA 205053] and 2132-1 [NDA 205596]). Under the PMRs, Merck was required to conduct a trial in patients, ages 2 to < 18 years, to evaluate the pharmacokinetic, safety and tolerability of two new formulations of posaconazole (intravenous solution and/or new age appropriate oral formulation) in immunocompromised pediatric patients with known or expected neutropenia (PMRs 2090-2 [NDA 205053] and 2132-2 [NDA 205596]), and to conduct a comparative, double-blind, randomized, multi-center trial, in patients ages 2 to < 18 years, to evaluate the safety, efficacy, and tolerability of posaconazole for prophylaxis of invasive fungal infections in pediatric patients with known or expected neutropenia. Thus, in this supplement, Merck proposes a new oral dosage formulation (for delayed-release oral suspension) for patients ages 2 to < 18 years to support the pediatric indication for prophylaxis of invasive Aspergillus and Candida infections in patients 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. Of note, the proposed for delayed-release oral suspension is not

bioequivalent on a mg-to-mg basis with the currently marketed oral suspension formulations.

We note that there were previous discussions between FDA and Merck, in which FDA provided agreement with Merck's proposed filing strategy to support the above-mentioned PMRs by submitting a supplemental NDA (NDA 205596 S-012) for the clinical and labeling information and a new NDA (NDA 214770) for the posaconazole powder for delayed-release oral suspension CMC information. NDA 214770 also includes the HF Engineering Summary Report.

Merck submitted a HF validation study protocol under IND 125097 on February 15, 2019. We identified deficiencies in the protocol and communicated the deficiencies to Merck on April 16, 2019.[1] On May 10, 2019, Merck submitted a response to Agency advice that we previously provided for their HF validation study protocol. We found that their proposed responses to our previous recommendations were reasonable.[2] Merck implemented our proposed recommendations prior to conducting their HF validation study.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

[1] Purcell, J. Human Factors Validation Study Protocol for Noxafil (IND 125097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 12. RCM No.: 2019-264.

[2] Purcell, J. Human Factors Memorandum for Noxafil (IND 125097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 15. RCM No.: 2019-264-1.

The sections below provide a summary of the study design, errors/close calls/use difficulties observed (Table 2), and our analysis to determine if the results indicate that the user interface is designed to support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

The HF validation study included a total of 51 untrained participants in the following user groups: 15 lay caregivers, 15 nurses, 21 pharmacists (16 hospital pharmacists, 5 retail pharmacists). The study environment represented a home environment for the lay caregiver participants, and a clinical setting for the nurse and pharmacist participants. The study tested the intend-to-market user interface.

Two dose volume scenarios were presented in the study, a 2.5 mL dose volume and an 8 mL dose volume. Presentation of the dose volumes was counterbalanced between participants within user groups. During the assessment, lay-caregiver and nurse participants were first asked to prepare and administer a prescribed dose to a pediatric manikin. Afterwards, participants were asked to draw up a second prescribed dose from an already prepared suspension. The study design for pharmacists differed from lay-caregivers and nurses reflecting their different roles and responsibilities regarding product use. Hospital pharmacists were asked to prepare and measure a prescribed dose according to a prescription order, and then were asked to draw up a second prescribed dose from an already prepared suspension whereas retail pharmacists did not prepare or measure medication. Retail pharmacists were only asked two knowledge based questions regarding appropriate preparation and dispensing of the product. All participants (including retail pharmacists) were asked knowledge task questions and probed for the root cause for any use related issues that occurred. Afterwards, participants were asked subjective feedback questions.

3.2 RESULTS AND ANALYSES

Table 2 describes the study results, Merck's analyses of the results, and DMEPA's analyses and recommendations for critical tasks where use errors or difficulties were observed and further risk mitigation strategies are recommended by DMEPA. We note that two hospital pharmacist participants (Hp06 and Hp09) did not complete all steps in the simulation due to study artifact. The details of the study artifacts are included as footnotes for each corresponding task in Table 2 below. Furthermore, we note that due to confusion in the interpretation of a CPOE order, two participants confused the strength as the prescribed dose of the product (i.e., instead of seeing that the dose for the scenario was a volume of 2.5 mL or 8 mL, these two participants instead interpreted the dose as 300 mg for the entire study). This initial confusion led to repeated task errors related to identifying the correct dose, measuring the correct dose, and withdrawing the correct dose as seen in Table 2 below.

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Knows the IFU contains information to use the Product (knowledge)	Caregivers, Nurses and Hospital Pharmacists (n=46)	UD=2	UD: (Hp03, Hp09) Initially thought the IFU was only for lay caregivers.	Normally refer to the PI for a product's information. These two hospital pharmacist participants may have thought it was only for lay caregivers and not for caregivers generally.	Despite the initial confusion, both participants eventually determined that the IFU contained preparation instructions. No additional risk mitigation is needed.	Based on the Applicant's task analysis and use error analysis (TA/UEA) if a user does not read the IFU there is a risk that the medicine will be prepared or administered incorrectly. This could potentially result in the introduction of pathogens in the product prior to administration to the patient or may lead to an underdose, overdose or missed dose. Our review of the study results identified subjective feedback in which the hospital pharmacists noted that the front of the IFU says "Instructions for Use for caregivers of toddlers and children" which may imply that it is not for healthcare providers. We are concerned that other healthcare providers may overlook the IFU as well. **Therefore, we provide IFU recommendation #1 in section 4 below for the Applicant to revise the title to "Instructions for Use for caregivers and healthcare providers of toddlers and children"**. We find this revision can be implemented without the need for submission of additional HF validation data.

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Shakes or settles powder to the bottom of the sachet) (observation)	Caregiver, nurse, Hospital Pharmacists (n=46)	UE=3	UE (Cg01): Did not shake or settle powder to the bottom of the sachet	Step 3 image does not look like shaking and missed the text.	To facilitate users in preparation of the dose, cut-line and scissors icons are provided on the sachet. The IFU instructs users to cut the sachet along the cutting line to open and gain access to the medication. All participants correctly cut open the sachet and successfully added the medication into the mixing cup. No additional risk mitigation is needed.	Based on the Applicant's TA/UEA if the user does not let the medicine settle to the bottom of the sachet there is a risk of product spillage after opening leading to an underdose or missed dose. We reviewed the study results and identified subjective feedback from participants who noted that they did not shake first based on the way the text was presented in the IFU. The Applicant asserts that the icons and instructions for cutting the sachet are included in the IFU but did not address the concerns related to the icons and text for shaking that were noted in the root cause analysis. We disagree that no additional risk mitigation is needed because the IFU can be improved by re-orienting the information to more clearly show that the user should shake the package prior to cutting it open. **Therefore, we provide IFU recommendation # 2 in section 4 below for the Applicant to reformat the icon and text related to shaking the packet so that the user sees this instruction first**. We find this revision can be implemented without the need for submission of additional HF validation data.
			UE (Nu15): Did not shake or settle powder to the bottom of the sachet	Did not think shaking was necessary		
			UE (Hp12): Shook the sachet after cutting it open	Initially missed the text instruction.		

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Shake the mixing liquid bottle (observation)	Caregiver, nurse, Hospital Pharmacists (n=46)	UE=1	UE (Hp12): Did not shake the mixing liquid	The participant forgot to shake the bottle.	The use event is less likely to occur once pharmacists become more familiar with the product preparation process. No additional risk mitigation is needed.	Based on the Applicant's TA/UEA if the mixing liquid bottle is not shaken there is a risk that the performance of the mixing liquid is compromised which may lead to underdose, overdose or missed dose. We agree with the Applicant's assertion that the use event is less likely to occur once the pharmacist becomes familiar with the preparation process. However, we note that the instruction to "Shake well before use" is included on the side panel of the mixing liquid bottle, which may be overlooked. **Therefore, we provide mixing liquid bottle recommendation # 1 in section 4 below for the Applicant to add the statement "Shake well before use" to the principal display panel (PDP) to increase the visibility of this important instruction**. We find this revision can be implemented without the need for submission of additional HF validation data.
Using the 10 mL blue syringe,	Caregiver, nurse, Hospital	UE=2 CC=1 UD=1	UE (Hp09): Poured mixing	Thought the dose was 300 mg and participant noted	Once the PI is updated with detailed dosing	Based on the Applicants TA/UEA, if the measurement is made to the wrong line or if a user does not use a syringe to measure the mixing liquid, the concentration of the oral

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
measure mixing liquid to the 9 mL line (observation)	Pharmacists (n=46)		liquid directly from the mixing liquid bottle into the mixing cup.	that she thought the IFU was for caregivers and she would normally look at PI for instructions on how to prepare a suspension.	information, e.g. dosing table, pharmacists will be able to have a better understanding of the preparation process - only portion of the total concentration will be administered based on detailed dosing information in PI.	suspension may be too low or too high leading to underdose, overdose or missed dose. We reviewed the study results and identified subjective feedback from two participants who thought the dose was 300 mg instead of 2.5 mL. Based on the root cause analysis and further follow up with Merck in an information request, it appears that the confusion with the dose was due to the way the strength was presented on the CPOE order screen. Furthermore, we note that the presentation of the strength (300 mg) and dose (2.5 mL or 8.0 mL) may have contributed to the errors as some participants noted that they are used to seeing the dose in milligrams. We also note that the lack of understanding that the IFU was an appropriate resource for healthcare providers also contributed to the use difficulties observed. We are concerned that other healthcare providers may overlook the IFU as well. **Therefore, we provide IFU recommendation #1 in section 4 below for the Applicant to revise the title to "Instructions for Use for caregivers and healthcare providers of toddlers and children"**. We
			UE (Nu07): Measured 6 mL of mixing liquid	Read the upside-down 6 as a 9	Delivering a more concentrated drug suspension in this case would result in an overdose of approximately 40% over the prescribed dose, which has a	

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
					low likelihood that the associated potential hazard/ harm to the patient would occur. The participant understood 9mL is required. The misreading of the number upside down is less likely to occur frequently. No additional risk mitigation is needed.	find this revision can be implemented without the need for submission of additional HF validation data. We also determined that further clarity is needed in the PI for healthcare professional users to support appropriate dosage and administration. Specifically, we determined that more detailed information should be included to further mitigate residual risk. **Therefore, we provide Prescribing Information recommendation # 3 in section 4 below for the Applicant to included more detailed information to alert the healthcare provider that only a portion of the total product should be administered to the patient**. We find this revision can be implemented without the need for submission of additional HF validation data. We also note that one participant misread the syringe and confused the 9 mL marking with the 6 mL marking. While this use error would have led to a more concentrated product and potentially an overdose, we note that the orientation and numbers on the proposed syringe are similar to other currently marketed syringes that are used for oral administration. Furthermore, we agree with
			CC (Hp03): Measured 2.5 mL of mixing liquid during first attempt, measured 9	Thought the 2.5 mL dose volume was the mixing liquid volume as well, 300 mg was the dose.	Once the PI is updated with detailed dosing information, e.g. dosing table, pharmacists will	

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			mL during second attempt		be able to have a better understanding of the preparation process - only portion of the total concentration will be administered based on detailed dosing information in PI.	Merck's Table 19 summary of postvalidation changes (see Appendix D). Therefore, we find the residual risk acceptable and do not have recommendations at this time.
			UD (Cg13): Reported difficulty pulling back plunger to 9 mL	Plunger must be pulled back with one hand and has small hands.	Despite the difficulty, the caregiver successfully withdrew 9 mL mixing liquid. No additional risk mitigation is needed.	

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Find dose amount (observation)	Caregiver, nurse, Hospital Pharmacists (n=46[3])	UE=4 CC=1	UE (Hp09): Did not find dose volume (2.5 mL dose)	Thought the dose was 300 mg and did not read IFU because thought it was for lay caregivers	Once the PI is updated with detailed dosing information, e.g. dosing table, pharmacists will be able to have a better understanding of the preparation process - only portion of the total concentration will be administered based on detailed dosing information in PI. Refer to Item 1 of Table 19 Summary of postvalidation changes.	Based on the Applicant's TA/UEA, if the dose is not identified and the user assumes an amount other than the prescribed dose there is a risk of overdose, underdose or missed dose. We reviewed the results of the HF study and identified subjective feedback from several participants experiencing use errors who thought that the dose was 300 mg. Refer to analysis previously noted for the task "Using the 10 mL blue syringe, measure mixing liquid to the 9 mL line". **We provide Prescribing Information recommendation # 3 in section 4 below for the Applicant to inform users that only a portion of the total product should be administered**. We find this revision can be implemented without the need for submission of additional HF validation data. Furthermore, we agree with Merck's Table 19 summary of postvalidation changes (see Appendix D).
			UE (Nu12): Reported confusion about dose volume (2.5 mL dose)	Thought the dose was 300 mg		
			UE (Nu12, Hp09): Initially read 0.8 mL, later read 8.0 mL in order to deliver 300 mg (8.0	Misread dose, thought dose was 300 mg		

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			mL dose)			
			CC (Hp14): Reported confusion about dose volume, self-corrected (8.0 mL)	Initially thought dose was 300mg, IFU corrected.	Despite the confusion, the participant self corrected by reading the IFU that there would be some suspension left in the mixing cup. In addition, once the PI is updated with detailed dosing information, e.g.	

[3] 1 participant (Hp06) assessment was excluded due to test artifact. The participant stated the Prescription Order was an incomplete order because it does not specify the concentration or the number of milligrams for the dose. Said would refer to PI for more information regarding concentration. Said 8 mL does not mean anything to him

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
					dosing table, pharmacists will be able to have a better understanding of the preparation process - only portion of the total concentration will be administered based on detailed dosing information in PI. Refer to Item 1 of Table 19 Summary of postvalidation changes.	
Find dose amount (knowledge)	Caregiver, nurse, Hospital	UE=1	UE (Hp09): Answered the Product says 300 mg	Thought the dose was 300 mg and participant did not read the IFU	Once the PI is updated with detailed dosing	Based on the Applicant's TA/UEA, if the dose is not identified and the user assumes an amount other than the prescribed dose there is a risk of overdose, underdose or missed dose.

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	Pharmacists (n=46[4])			during the scenario	information, e.g. dosing table, pharmacists will be able to have a better understanding of the preparation process - only portion of the total concentration will be administered based on detailed dosing information in PI. Refer to Item 1 of Table 19 Summary of postvalidation changes.	We reviewed the results of the HF study and identified subjective feedback from the participant experiencing this use error who thought that the dose was 300 mg and noted that the prescription did not indicate the dose in mg. Refer to our analysis previously noted for the task "Using the 10 mL blue syringe, measure mixing liquid to the 9 mL line". We also note that the lack of understanding that the IFU was an appropriate resource for healthcare providers also contributed to the use difficulties observed. We are concerned that other healthcare providers may overlook the IFU as well. **Therefore, we provide IFU recommendation #1 in section 4 below for the Applicant to revise the title to "Instructions for Use for caregivers and healthcare providers of toddlers and children"**. We find this revision can be implemented without the need for submission of additional HF validation data.

[4] 1 Participant (Hp06) assessment was excluded due to test artifact. Said he needed the mg dose information.

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
						We provide Prescribing Information recommendation # 3 in section 4 below for the Applicant to included more detailed information to alert the healthcare provider that only a portion of the total product should be administered to the patient. We find this revision can be implemented without the need for submission of additional HF validation data. Furthermore, we agree with Merck's Table 19 summary of postvalidation changes (see Appendix D).
Select the appropriate syringe: the 3 mL syringe for the 2.5 mL	Caregiver, nurse, Hospital Pharmacists (n=46[5])	UE=1 CC=2	UE (Hp09): Selected 10 mL syringe for 2.5 mL dose	Thought the dose was 300 mg	Once the PI is updated with detailed dosing information, e.g. dosing table, pharmacists will be	Based on the Applicant's TA/UEA, if the dose is not identified and the user assumes an amount other than the prescribed dose there is a risk of overdose, underdose or missed dose. We reviewed the results of the HF study and identified

[5] 1 participant (Hp06) was excluded in the assessment due to test artifact. Said would not dispense the medication because he does not know what the dose is in mg and the PI was not prepared for the study.

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
10 mL syringe for the 8.0 mL dose(observation)					able to have a better understanding of the preparation process -only portion of the total concentration will be administered based on detailed dosing information in PI. Refer to Item 1 of Table 19 Summary of postvalidation changes.	use error who thought that the dose was 300 mg and wanted to draw up as much suspension as possible out of the mixing cup. Based on the root cause analysis it appeared that the confusion with the dose was due to the way the strength was presented on the CPOE order. Refer to our analysis previously noted for the task "Using the 10 mL blue syringe, measure mixing liquid to the 9 mL line". **We provide Prescribing Information recommendation # 3 in section 4 below for the Applicant to included more detailed information to alert the healthcare provider that only a portion of the total product should be administered to the patient.** We find this revision can be implemented without the need for submission of additional HF validation data. Furthermore, we agree with Merck's Table 19 summary of postvalidation changes (see Appendix D).
			CC (Nu12, Hp09): Initially selected 3 mL syringe for 8.0 mL dose, self-corrected	Misread the dose as 0.8 mL	Despite the confusion, the participants self corrected and chose the correct size of the syringe.	

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
					No additional risk mitigation is needed.	
Select the appropriate syringe: Knows to only use the syringes in the kit for measuring and administering the medication) (knowledge)	Caregiver, nurse, Hospital Pharmacists (n=46)	UE=24	UE (Cg02, Cg04, Cg06, Cg11, Cg12, Cg13, Cg15, Nu01, Nu08, Nu12, Hp01, Hp02, Hp03, Hp09, Hp10, Hp12, Hp13, Hp14, Hp15, Hp16): Answered could use other oral syringes	Did not understand IFU was saying do not use other syringes or why to only use the kit syringes	Caregivers understood the syringes provided with the kit need to be reused. In the case of the kit being used in a clinical environment, additional notched-tip syringes will be provided. Furthermore, once the PI is updated with information about the notched-tip syringe design and associated rationale, HCPs will	Based on the Applicant's TA/UEA, if the user uses a syringe other than the notched-tip syringes provided in the kit there is a potential for the drug to clump in the syringe tip. This may result in the child receiving less than the prescribed dose which may lead to under dose or missed dose. We reviewed the study results and noted that several participants did not understand why you could not use other syringes and did not think the IFU was clear about only using the notched-tip syringe. While we agree that in the clinical environment there will be additional notched-tip syringes provided, this is not the case for lay caregivers. **<u>Therefore, we provide IFU recommendation # 3 in section 4 below for the Applicant to specify the information regarding the notched tip syringes in the IFU</u>**. We find this revision can be implemented without the need for submission of additional HF validation data.
			UE (Nu07, Hp07, Hp08): Answered could use	Did not notice the information on page 14		

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			other oral syringes		have a better understanding of the need to only use the provided notched- tip syringe. PI will also include information about the risk of using regular syringe (i.e. aggregation). This will help HCPs in terms of identifying and mitigating the occurrence of the aggregation. Refer to item 2 and 3 in Table 19, Summary of post-validation changes.	Furthermore, we agree with Merck's Table 19 summary of postvalidation changes (see Appendix D).
			UE(Nu10): Answered could use other oral syringes	Does not reuse supplies in hospital environment		

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			(Hp11): Answered IFU was not clear whether other oral syringes could be used	Did not understand IFU was saying do not use other syringes or why to only use the kit syringes	Additional notched-tip syringes will be provided. Furthermore, once the PI is updated with information about the notched-tip syringe design and associated rationale, HCPs will have a better understanding of the need to only use the provided notched- tip syringe. PI will also include information about the risk of using regular syringe (i.e. aggregation). This will help HCPs in	
			UE (Nu04): Answered would use provided oral syringes, but could not use the kit	Does not reuse supplies in hospital environment		

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
					terms of identifying and mitigating the occurrence of the aggregation. Refer to item 2 and 3 in Table 19, Summary of post-validation changes.	
Fill syringe with correct dose/volume (2.5 mL) (observation)	Caregiver, nurse, Hospital Pharmacists (n=46[6])	UE=1	UE (Hp09): Drew up over 10 mL of suspension (2.5 mL dose)	Thought the dose was 300 mg.	Once the PI is updated with detailed dosing information, e.g. dosing table, pharmacists will	Based on the Applicant's TA/UEA, if the dose is not identified and the user assumes an amount other than the prescribed dose there is a risk of overdose, underdose or missed dose. We reviewed the results of the HF study and identified subjective feedback from the participant experiencing this

[6] 1 participant (Hp06) was excluded from assessment due to test artifact. Said would not dispense the medication because he does not know what the dose is in mg and the PI was not prepared for the study

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
					be able to have a better understanding of the preparation process - only portion of the total concentration will be administered based on detailed dosing information in PI. Refer to Item 1 of Table 19 Summary of postvalidation changes.	use error who thought that the dose was 300 mg and wanted to draw up as much suspension as possible out of the mixing cup. Furthermore, this participant did not read the IFU because they thought that it was only intended for lay caregivers. Based on the root cause analysis it appeared that the confusion with the dose was due to the way the strength was presented on the CPOE order. Refer to our analysis previously noted for the task "Using the 10 mL blue syringe, measure mixing liquid to the 9 mL line". We are concerned that other healthcare providers may overlook the IFU. **Therefore, we provide IFU recommendation #1 in section 4 below for the Applicant to revise the title to "Instructions for Use for caregivers and healthcare providers of toddlers and children"**. We find this revision can be implemented without the need for submission of additional HF validation data. **We provide Prescribing Information recommendation # 3 in section 4 below for the Applicant to included more detailed information to alert the healthcare provider that only a portion of the total product should be administered**

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
						to the patient. We find this revision can be implemented without the need for submission of additional HF validation data. Furthermore, we agree with Merck's Table 19 summary of postvalidation changes (see Appendix D).
Fill syringe with correct dose/ Volume: Knows that not all of the suspension will be used (knowledge)	Caregiver, nurse, Hospital Pharmacists (n=46)	UE=1	UE (Nu12): Answered that there will not be suspension left in the mixing cup	Thought the dose was 300 mg.	Once the PI is updated with detailed dosing information, e.g. dosing table, pharmacists will be able to have a better understanding of the preparation process - only portion of the total concentration will be administered based on detailed	Based on the Applicant's TA/UEA, if the dose is not identified and the user assumes an amount other than the prescribed dose there is a risk of overdose, underdose or missed dose. We reviewed the results of the HF study and identified subjective feedback from the participant experiencing this use error who noted that the sachet says 300 mg and the name of the medication says "(300 mg)" so she thought that was the dose. Based on the root cause analysis it appeared that the confusion with the dose was due to the way the strength was presented on the CPOE order. Refer to our analysis previously noted for the task "Using the 10 mL blue syringe, measure mixing liquid to the 9 mL line".

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
					dosing information in PI. Refer to Item 1 of Table 19 Summary of postvalidation changes.	**We provide Prescribing Information recommendation # 3 in section 4 below for the Applicant to included more detailed information to alert the healthcare provider that only a portion of the total product should be administered to the patient**. We find this revision can be implemented without the need for submission of additional HF validation data. Furthermore, we agree with Merck's Table 19 summary of postvalidation changes (see Appendix D).
Fill syringe with correct dose/volume (8 mL) (observation)	Caregiver, nurse, Hospital Pharmacists (n=46[7])	UE=2 CC=1 UD=2	UE (Nu12, Hp09): Initially measured 0.8 mL, later measured 8.0	Thought the dose was 300 mg.	Once the PI is updated with detailed dosing information, e.g. dosing table, pharmacists will	Based on the Applicant's TA/UEA, if the dose is not identified and the user assumes an amount other than the prescribed dose there is a risk of overdose, underdose or missed dose. We reviewed the results of the HF study and identified

[7] 1 participant (Hp06) was excluded from assessment due to test artifact. Said he reconstituted 300 mg with 9 mL of mixing liquid and the Order says 300 mg for the strength, so he drew up all 300 mg. Said he would not send it to the floor though because he does not understand why the prescription says 8.0 mL and he could not read the PI for information regarding the concentration. The PI was not available for the study.

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			mL in order to deliver 300 mg (8.0 mL)		be able to have a better understanding of the preparation process - only portion of the total concentration will be administered based on detailed dosing information in PI. Refer to Item 1 of Table 19 Summary of postvalidation changes.	subjective feedback from the participants experiencing this use error who thought that the dose was 300 mg. Based on the root cause analysis it appeared that the confusion with the dose was due to the way the strength was presented on the CPOE order. Refer to our analysis previously noted for the task "Using the 10 mL blue syringe, measure mixing liquid to the 9 mL line". **We provide Prescribing Information recommendation # 3 in section 4 below for the Applicant to included more detailed information to alert the healthcare provider that only a portion of the total product should be administered to the patient**. We find this revision can be implemented without the need for submission of additional HF validation data.
			CC: (Cg 13): Drew up 6 mL of suspension and 4 mL of air, self-corrected	Notches were not submerged in the suspension	Despite the error at the beginning, the participant self-corrected and drew 8mL suspension in syringe. No additional risk	Another participant recorded as experiencing a use difficulty struggled to draw up 8 mL of suspension. The participant corrected with help. We reviewed the subjective feedback which described that the participant was tilting the mixing cup, but since the notches of the oral syringe were not completely submerged in the suspension,

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			(8.0 mL)		mitigation is needed.	air was being drawn into the syringe. The participant repeatedly attempted to draw up suspension and requested assistance from a colleague. The Moderator instructed the participant to put the syringe tip down into the corner of the tilted mixing cup and the participant was then able to draw up the dose. The participant said she did not notice the instruction on page 15 to put the tip into the lowest part of the cup. While we acknowledge this feedback, in this instance we determined the residual risk is acceptable when taking into account Merck's Table 19 summary of postvalidation changes (see Appendix D). We have no further recommendations.
			UD (Nu08): Struggled to draw up 8.0 mL of suspension, corrected with help (8.0 mL)		Despite the difficulty at the beginning, the Participant corrected with help and drew 8mL suspension in syringe. The participant is a nurse and will be able to find help as needed in a clinical environment. No additional risk mitigation is needed.	
			UD (Hp08): Reported confusion	Step 5 and Step 11 images for filling a syringe are different	Despite the confusion, the participant	

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			about top Step 11 image		successfully drew 8mL suspension in the syringe. No additional risk mitigation is needed.	
Check and remove air bubbles (8 mL) (observation)	Caregiver, nurse, Hospital Pharmacists (n=46[8])	UE=7 CC=2 UD=1	Use error (Nu07, Nu08): Did not remove almost 1 mL of air (8.0 mL dose)	Did not notice air and residual suspension remained in the top of the syringe barrel.	The impact on the delivered dose was not significant (i.e. decreased dose by <15% of prescribed dose). There is a low likelihood that the associated potential hazard/harm to the patient would occur.	Based on the Applicant's TA/UEA if there are air bubbles still present in the syringe or if the volume in the syringe is not the prescribed amount after the bubble is removed, there is risk of the patient receiving an overdose, underdose or missed dose. We reviewed the HF study results and identified subjective feedback from participants experiencing use errors, close calls and use difficulties. Some of the errors were associated with users being unfamiliar with reading the measurements on the syringe and not thinking that air in the syringe tip (below the 1 mL mark) was significant. There

[8] 1 participant (Hp06) was excluded from assessment due to test artifact. Said would not dispense the medication because he does not know what the dose is in mg and the PI was not prepared for the study.

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
					No additional risk mitigation is needed.	was also subjective feedback related to the difficulty with removing air bubbles. As part of their RCA, the Applicant noted that the notches on the syringe may introduce more air into the syringe when drawing up larger doses and the viscosity of the suspension may make removing air bubbles more difficult. The Applicant also noted that these errors would have resulted in the patient receiving between 10% to 20% reduced dose which is not significant. We discussed the risk of use errors with this task with DAI, and DAI expressed concern that up to a 20% loss of dose could result in underdose leading to reduced efficacy. Additionally, to account for the potential for up to 20% underdose, the Clinical Pharmacology reviewer proposed a dose banding approach in which a higher dose would be
			UE (Cg11, Nu10): Did not remove almost 1 mL of air (8.0 mL dose)	Estimated the suspension volume visually	The impact on the delivered dose was not significant. The dosing error due to visual estimation by participants is estimated to be less than +/-20% of the prescribed dose. There is a low likelihood that the	

[9] Response to Agency Questions (posaconazole NDA 214770). Whitehouse Station (NJ): Merck Sharp & Dohme Corp.; 2021 APR 21. Available from: \\CDSESUB1\evsprod\nda214770\0028\m1\us\quality-information-amendment-22apr2021.pdf

[10] Response to FDA regarding dose for PFS (posaconazole NDA 205596 S-012). Whitehouse Station (NJ): Merck Sharp & Dohme Corp.; 2021 APR 21. Available from: \\CDSESUB1\evsprod\nda205596\0115\m1\us\clinical-information-amendment-22apr2021.pdf

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
					associated potential hazard/harm to the patient would occur. No additional risk mitigation is needed.	administered to certain patients who would have low exposure. Following discussion at an April 8, 2021 teleconference, Merck submitted their revised HF study report (see Appendix D) and clarified that "up to 20% less than the prescribed dose was used as a bracketing estimation in assessing the risk of use error associated with the task "check and remove air bubbles" after measuring the 8 mL dose. In the Human Factors (HF) validation study, the largest error observed with the task "check and remove air bubbles" after measuring the 8 mL was 12.5%. The Human Factors Summary Report was revised based on the actual errors observed."[9] Merck also provided a revised dose banding table for pediatric patients.[10] Upon review, the Clinical Pharmacology team found the new proposed dosing table acceptable but recommended additional adjustments to the dosing table to account for the potential for 12.5% reduced dose due to air bubbles. We defer to DIA on the acceptability of the proposed dosing tables. We acknowledge the dosing has been revised to mitigate the risk of underdose. However, we recommend additional labeling mitigations to the IFU. **Therefore, we provide IFU**
			UE (Cg04, Cg10): Did not remove almost 0.5 mL of air (8.0 mL dose)	Thought the measurement was from the 1 mL to the 8.0 mL graduation marks.	The impact on the delivered dose was not significant (i.e. decreased dose by <10% of prescribed dose). There is a low likelihood that the associated potential hazard/harm to the patient would occur. No additional risk mitigation is needed.	
			Use error: (Cg12): Did not remove almost 0.5 mL of air (8.0 mL dose)	Thought the amount of air was acceptable		

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			CC (Cg01): Struggled to remove air bubbles, drew up volume again (8.0 mL dose)	Notches may introduce more air into the syringe when drawing up larger doses and viscosity of suspension may make removing air bubbles more difficult	Despite the difficulty, the participant was successful in air bubble removal and drawing up 8mL suspension in syringe. No additional risk mitigation is needed.	**recommendation # 4 in section 4 below for the Applicant to update the IFU to emphasize the importance of removing air bubbles and air gaps as well as to better inform users of how to identify and remove air gaps in the syringe**. We find this revision can be implemented without the need for submission of additional HF validation data.
			CC (Cg13): Struggled to remove 4 mL of air, self corrected (8.0 mL dose)	Initially forgot how to remove air bubbles		

Table 2: Summary and Analyses of Study Results						
Critical Tasks (observed or knowledge)	**User Group completing Task**	**Number of Use Errors (UE), Use Difficulties (UD) and Close Calls (CC)**	**Description of UE, UD and CC**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			UD (Hp01): Reported it was difficult to remove air bubbles (8.0 mL dose)	Did not want to lose medication when expelling air bubbles		

ANALYSIS OF OTHER CRITICAL TASKS AND NON-CRITICAL TASKS

We note that the results of the HF validation study showed use errors (e.g. failures, difficulties, and close calls) with additional critical tasks not included in Table 2 above. It is important to note that in our analysis, we do not agree that all tasks identified by Merck as "critical" are in fact critical tasks. However, for the purposes of this review we determined that no further follow up to recategorize the tasks is needed at this time. We also identified use errors (e.g. failures, difficulties, and close calls) with non-critical tasks. The following list of critical and non-critical tasks represent those where we determined that the residual risk is acceptable without further need for risk mitigation strategies.

- Call the doctor for any questions (knowledge)
- Verify all components are present and free of damages (knowledge)
- Confirm mixing cup is clean and empty (knowledge)
- Open the sachet when ready to prepare the dose (knowledge)
- Add medicine to mixing cup (observation)
- Only use the mixing liquid to make the suspension (knowledge)

- Check and remove air bubbles while measuring the mixing liquid (observation)
- Shakes the mixing cup, without spilling, until powder is suspended and there are no clumps (observation)
- Continues shaking the mixing cup if clumps are present (observation and knowledge)
- Check and remove air bubbles for the 2.5 mL dose (observation)
- If necessary, pulls back plunger to dose volume mark 8 mL (observation)
- If patient spits up asks the doctor what to do (knowledge)
- Wash hands (observation)
- Confirm product expiration dates have not lapsed (observation and knowledge)
- Dispose of medicine in the trash (knowledge)
- Clean components (syringe and cup) (knowledge)
- Store product kit (knowledge)

4 LABELS AND LABELING

During our previous review of the posaconazole HF validation study protocol we noted that the currently marketed Noxafil oral suspension and oral tablet are indicated for ages 13 and older. Because Merck's proposed for delayed-release oral suspension is indicated for pediatric patients between the ages of 2 years old to less than 18 years old, these three products have an overlap in patient population between the ages of 13 years old to less than 18 years old. Due to this overlap in patient population, we were concerned about confusion amongst prescribers related to selecting the appropriate product for a patient in this age group. Furthermore, since the oral suspension and for delayed-release oral suspension have different concentrations (40 mg/mL vs. 30 mg/mL once mixed) and are not substitutable because they are not bioequivalent on a mg to mg basis, we are concerned of the risk of medication errors related to dispensing the correct product.

In our review of the HF validation study protocol[11] we requested that Merck ensure that they have considered these risks and have implemented appropriate mitigation strategies to differentiate these products to reduce the risk of confusion and medication errors. As part of the NDA submission, Merck provided revised carton labeling for the currently marketed Noxafil oral suspension to include the statement "Attention: Noxafil Oral Suspension is NOT [redacted] (b) (4) with Noxafil Delayed-Release Tablets or Noxafil Powder for Delayed-Release Oral Suspension due to differences in the dosing of each formulation." We also note that in our proprietary name review, the proposed name, Noxafil, was denied due to concerns regarding the lack of a modifier to help distinguish the powder for delayed-release oral suspension from the currently marketed oral suspension.[12] Subsequently, on February 2, 2021, Merck submitted the name, Noxafil PowderMix for review. On April 30, 2021 we found the name, Noxafil PowderMix, conditionally acceptable.[13] We find that the addition of a modifier as well as the proposed carton labeling statement to alert healthcare providers will help to reduce the risk of confusion between the different formulations.

Tables 3 and 4 below include the identified medication error issues with the submitted labels and labeling our rationale for concern, and the proposed recommendation to minimize the risk for medication error for the labels and labeling submitted under NDA 205596 S-012. Our evaluation of the proposed Noxafil prescribing information submitted under NDA 205596 S-013 did not identify areas of vulnerability that may lead to medication errors.

[11] Purcell, J. Human Factors Validation Study Protocol for Noxafil (IND 125097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 12. RCM No.: 2019-264.

[12] Myers, D. Proprietary Name Review for Noxafil (NDA 214770). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 03. Panorama #: 2020-41831928.

[13] Myers, D. Proprietary Name Review for Noxafil (NDA 214770). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 30. PNR ID #: 2021-10447273792.

Table 3: Identified Issues and Recommendations for Division of Anti-Infective Products (DAI)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
General Issues			
1.	The term [redacted] " is used to convey that the oral suspension formulation cannot be substituted with the delayed-release tablet or for delayed-release oral suspension.	[redacted]	We recommend revising this statement by removing the term [redacted] " and replacing it with the term "substitutable". For example: Noxafil oral suspension is not substitutable with Noxafil delayed-release tablets or for delayed-release oral suspension due to the differences in the dosing of each formulation." Furthermore, to ensure that users do not overlook this important information when reviewing the Dosage for the different formulations we recommend that this statement is repeated at the beginning of sections 2.2 Adult Patients and 2.3 Pediatric Patients.
Highlights of Prescribing Information			
1.	The Dosage and Administration instructions in the Highlights includes complex dosing information in bullet format for the pediatric population.	The Highlights appear cluttered and the bulleted format of the Dosage and Administration for pediatrics may reduce readability of this complex dosing.	We recommend revising the pediatric dosing information in the Highlights and including a cross-reference to the dosing information in the FPI. For example, revise this section to read: [redacted]

[redacted]

			(b) (4) [redacted]
Full Prescribing Information			
1.	Table 2 in the Dosage and Administration section appears cluttered as it includes all 4 formulations within the same table. We note that the dosing for each formulation is dependent on different factors (i.e. age, weight, indication).	As currently presented, we are concerned that users may confuse the dosing for the different formulations which may lead to product selection medication errors. Furthermore, the for delayed-release oral suspension and delayed-release tablet should not be substituted on a mg to mg basis with the oral suspension. Therefore, if confused, this may lead to the patient receiving an incorrect dose if the for delayed-release oral suspension and delayed-release tablet formulations	To reduce the risk of confusion and medication errors, we recommend that the formulations are divided into separate tables. For example, include the for delayed-release oral suspension in Table 2; the delayed-release tablet and injection in Table 3, and the oral suspension in table 4. We provide our revisions in tracked changes in Appendix F below.

		are substituted for the oral suspension.	
2.	Section 2.7 Preparation and Administration Instructions for Noxafil for Delayed-Release Oral Suspension (children ages 2 to less than 18 years of age) includes the instruction "The mixing cup should be hand washed and reused."	We note that in the HF validation study several healthcare provider participants stated that it is uncommon practice to wash and reuse mixing cups/syringes in the hospital setting. Because the PI is directed towards healthcare providers this sentence should be revised to be more applicable to this user group and use environment.	Revise the statement to "The mixing cup may be hand washed and reused. Alternatively, the mixing cup may be discarded and a similar mixing cup may be used for subsequent doses."
3.	Section 2.7 Preparation and Administration Instructions for the Noxafil Powder for Delayed-Release Oral Suspension (children ages 2 to less than 18 years of age) does not advise the user that not all of the product in the mixing cup will be	We note that in the HF validation study two healthcare provider participants withdrew the incorrect volume of drug from the mixing cup. It appeared that the confusion was related to the presentation of the strength and dose on the prescription label and lack of understanding that the full contents would not be used for all patients. If a user	To reduce the risk of wrong dose errors, add the statement: "Not all of the Noxafil PowderMix in the mixing cup will be used. There will be some left over in the mixing cup." after the sentence, "Measure the prescribed dose volume with the notched tip syringe provided with the kit and administer the dose orally". Also, see recommendation #4 below.

	used for a single dose.	withdraws the full contents of the mixing cup into the syringe, the patient could receive the wrong dose leading to an overdose. Therefore, a statement could be added to the PI to further alert the healthcare provider that the full contents of the mixing cup will not be used for the patient.	
4.	In their submission, Merck noted that "The maximum dose volume that can be administered with the posaconazole PFS kit is 8 mL (corresponding to a maximum dose of 240 mg). This is due to the notch-tip oral dosing syringe design and usability considerations when preparing the dose to a numbered graduation mark on the notch-tip oral	This important information is not included in the PI. This information is helpful to alert the healthcare provider to the maximum amount of drug that can be withdrawn after reconstitution.	Add the following: "The maximum dose that can be accurately withdrawn from the mixing cup after reconstitution is 240 mg (8 mL)." below the proposed statement in recommendation number 3 above. For example: • Measure the prescribed dose volume with the notched tip syringe provided with the kit and administer the dose orally • Not all of the Noxafil in the mixing cup will be used. There will be some left over in the mixing cup. • The maximum dose that can be accurately withdrawn from the mixing cup after reconstitution is 240 mg (8 mL)."

	dosing syringe, thereby reducing the probability of dosing errors.”		
5.	In section 16, How Supplied/Storage and Handling, the for delayed-release oral suspension is described as being supplied as package A and package B.	It is unclear if both packages will be distributed and supplied in the same carton/box or if they are supplied in separate boxes.	Clarify how the package A and package B will be supplied. For example, specify whether a box/carton will contain one each of package A and package B, whether a box/carton will contain several package A and package B, or whether package A and package B will be supplied in separate boxes/cartons. Section 16 should be updated accordingly.

Table 4: Identified Issues and Recommendations for Merck **Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.(entire table to be conveyed to Applicant)**			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Instructions for Use (IFU)			
1.	The IFU is titled "Instructions for Use for caregivers of toddlers and children", but it is intended for both lay caregivers and healthcare providers.	The results of the HF validation study included several use errors and use difficulties from nurses and pharmacists who did not read the IFU because the title was only directed towards caregivers. Not reading the IFU may result in preparation and administration medication errors.	Revise the title to "Instructions for Use for caregivers and healthcare providers of toddlers and children".
2.	On Page 7, Step 3 of the IFU, the location of the graphic of a user shaking a packet next to a table with scissors (left-hand side) and the associated text instruction (right-hand side) can be improved.	The results of the HF validation study included use errors in which the participants did not shake the packet because they did not notice the text instruction prior to cutting the packet open with scissors. Failure to shake the packet to ensure the medicine settles to the bottom prior to cutting open can lead to spillage of the product during opening and underdose/missed dose.	To clarify this step, we recommend that the location of the graphic and associated text are switched so that the text instruction is located on the left-hand side and the graphic on the right-hand side. For example, revise to: • Take **1 packet** of Noxafil and shake the powder to the bottom of the packet. 

3.	In “Before You Start” on Page 2 of the IFU, the statement “Measure the right dose using an oral syringe.” does not specify the type of oral syringe.	The results of the HF validation study showed that several participants did not understand that only the provided notched-tip syringes should be used to prepare and administer the dose. HF formative testing showed that using a standard oral syringe (without the notched-tip) resulted in drug clumping in the syringe tip. This may lead to an underdose or missed dose.	Revise the statement to read “Measure the right dose using the included notched-tip oral syringe. Only use the notched-tip syringes supplied with the kit. Do not use other oral syringes. ”
4.	IFU step 12 does not describe the importance of removing air bubbles and air gaps from the notched-tip syringe.	The results of the HF validation study showed several participants did not remove air bubbles prior to administering the dose because they thought that the amount of air in the syringe was acceptable. Furthermore, several participants did not remove air in the syringe because they did not realize that an air gap (i.e. space at top of the syringe barrel) was also an air bubble. Failure to remove air bubbles may result in the patient receiving an underdose which may impact efficacy.	Revise IFU Step 12 to include a statement to emphasize the importance of removing air bubbles from the notched-tip syringe. For example, “Be sure to follow the directions to remove air bubbles from the syringe. Air bubbles can affect the amount of medicine that the child gets.” Furthermore, revise IFU Step 12 to include a statement to emphasize that users should check for air gaps and residual suspension in the top of the syringe barrel (between tip and 1 mL). For example, revise the instructions to read as : “Hold the syringe with notched tip up. Tap it with your finger to move any air bubbles up. Check for air gaps in the tip of the syringe. Slowly push the plunger to make the air bubbles or air gaps come out.”

			We also recommend adding an image to IFU Step 12 which shows an air gap at the tip of the syringe and adding an arrow pointing to the top of the syringe
5.	There are several instances where the for delayed-release oral suspension is included as 'Noxafil' without the modifier 'PowderMix'.	Omitting the modifier, PowderMix, from the proprietary name in the labeling may lead to confusion and wrong drug medication errors between Noxafil PowderMix for delayed-release oral suspension and the Noxafil oral suspension.	Ensure that when referring to the for delayed-release oral suspension, that the proprietary name is always included as 'Noxafil PowderMix'.
Mixing Liquid bottle label			
1.	The statement "Shake well before use" is currently included on the side panel of the mixing liquid bottle.	The results of the HF validation study included a use error in which a participant did not shake the mixing liquid bottle. Not shaking the mixing liquid may result in compromised performance which can lead to underdose, overdose or missed dose.	To increase awareness of this important task, add the statement "Shake well before use" to the principal display panel (PDP).
2.	The mixing liquid label references the term "package insert".	The term "package insert" is inconsistent with the "prescribing information".	To ensure consistency with the prescribing information revise "package insert" to "prescribing information".
3.	As currently presented, the format for the	Certain formats may lead to confusion and increase the risk	To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the

	expiration date is not defined.	of deteriorated drug medication errors.	human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
4.	The mixing liquid does not include a statement that it is only intended as a mixing agent.	Including this information can serve as an additional reminder to users that the mixing liquid should be used for reconstituting the Noxafil PowderMix and does not contain the active ingredient.	Add the statement "For mixing only – mix with Noxafil PowderMix as directed" to the bottom of the PDP (if space permits) or on the side panel.
Carton labeling			
1.	Refer to mixing liquid label recommendation #3 and revise accordingly.		
2.	The carton labeling does not include a usual dose statement.	The usual dose statement is required per 21 CFR 201.55.	Revise the labeling to include the statement "Recommended Dosage: See prescribing information."

3.	The carton labeling includes references to the proprietary name 'Noxafil' without the modifier, 'PowderMix'. For example, the section entitled "Each Multi-Dose Kit (Package A) contains" includes the following: "8 packets of Noxafil" and "473 mL Mixing Liquid for Noxafil".	Omitting the modifier, PowderMix, from the proprietary name on the carton labeling may lead to confusion and wrong drug medication errors between Noxafil PowderMix for delayed-release oral suspension and the Noxafil oral suspension.	Add the modifier, PowderMix, so that the proprietary name is included as "Noxafil PowderMix". Therefore, revise to "8 packets of Noxafil PowderMix" and "473 mL Mixing Liquid for Noxafil PowderMix".
4.	The carton labeling does not include a 2D data matrix barcode.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[15] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

[15] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

		transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	
5.	The term [redacted] (b) (4) " is used to convey that the oral suspension formulation cannot be substituted with the delayed-release tablet or for delayed-release oral suspension.	[redacted] (b) (4)	We recommend revising this statement by removing the term [redacted] (b) (4) and replacing it with the term "substitutable "on the carton labeling for the Noxafil PowderMix for delayed-release oral suspension as well as for the Noxafil oral suspension. For example: Noxafil PowderMix for delayed-release oral suspension carton: "Noxafil PowderMix for Delayed-Release oral suspension is NOT substitutable with Noxafil Oral Suspension due to differences in the dosing of each formulation." Noxafil oral suspension carton: "Noxafil Oral Suspension is NOT substitutable with Noxafil PowderMix for Delayed-Release oral suspension due to differences in the dosing of each formulation."
Container (sachet) label			
1.	Refer to mixing liquid label recommendation #3 and revise accordingly.		
Patient Information			

[16] Guidance for Industry: Labeling for Biosimilar Products. 2018. Available from: https://www.fda.gov/media/96894/download

1.	Several sections within the Patient Information include the proprietary name 'Noxafil' without also including the proprietary name 'Noxafil PowderMix' when referring to information for all formulations. For example, "What are the possible side effects of Noxafil?"	Not including the proprietary name 'Noxafil PowderMix' when referring to information that is pertinent to that formulation may lead to confusion and misinterpretation.	Ensure that the proprietary name, 'Noxafil PowderMix' is included when referring to information that is pertinent to that formulation. For example, revise "What are the possible side effects of Noxafil?" to "What are the possible side effects of Noxafil and Noxafil PowderMix?". Furthermore, ensure that when only referring to the for delayed-release oral suspension, that the proprietary name is always included as 'Noxafil PowderMix'.

5. CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study identified use errors with critical tasks. Furthermore, our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We determined that additional risk mitigation strategies should be implemented to further reduce the residual risk associated with the design of the user interface. However, these strategies can be implemented without the submission of additional human factors. We provide recommendations that we advise are implemented prior to approval. Below, we have provided recommendations in Table 3 for the Division and Table 4 for Merck. We ask that the Division convey Table 4 in its entirety to Merck so that recommendations are implemented prior to approval of this NDA.

5.1 RECOMMENDATIONS FOR MERCK

The results of your human factors (HF) validation study indicated a need for further revisions to your user interface in order to mitigate residual risk. We acknowledge your proposed post-validation changes, which we find reasonable. However, we have provided recommendations in Table 4 and we recommend that you implement these recommendations prior to approval of this NDA. We have determined at this time that these revisions can be implemented without providing additional human factors data to support these revisions.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for posaconazole that Merck submitted on 2/12/2021.

Table 5. Relevant Product Information	
Initial Approval Date	November 25, 2013
Therapeutic Drug Class or New Drug Class	Anti-infective
Active Ingredient (Drug or Biologic)	posaconazole
Indication	Noxafil is an azole antifungal agent indicated for: •prophylaxis of invasive Aspergillus and Candida infections in patients 2 years of age and older 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. Oral suspension •treatment of oropharyngeal candidiasis (OPC), including OPC refractory (rOPC) to itraconazole and/or fluconazole
Route of Administration	Intravenous, oral
Dosage Form	Injection Delayed-release tablet Oral suspension For delayed-release oral suspension (proposed)
Strength	•injection: 300 mg per vial (18 mg per mL) •delayed-release tablet 100 mg •oral suspension 40 mg per mL •For delayed-release oral suspension 300 mg

<table>
<tr><td>Dose and Frequency</td><td><u>Adults:</u>
<table>
<tr><th>Indication</th><th>Dose and Duration of Therapy</th></tr>
<tr><td>Prophylaxis of invasive Aspergillus and Candida infections</td><td>Injection:

<u>Loading dose</u>: 300 mg Noxafil injection intravenously twice a day on the first day.

<u>Maintenance dose</u>: 300 mg Noxafil injection intravenously once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression.

Delayed-Release Tablets:

<u>Loading dose</u>: 300 mg (three 100 mg delayed-release tablets) twice a day on the first day.

<u>Maintenance dose</u>: 300 mg (three 100 mg delayed-release tablets) once a day, starting on the second day. Duration of therapy is based on recovery from neutropenia or immunosuppression.

Oral Suspension: 200 mg (5 mL) three times a day. Duration of therapy is based on recovery from neutropenia or immunosuppression.</td></tr>
<tr><td>Oropharyngeal Candidiasis (OPC)</td><td>Oral Suspension:
<u>Loading dose</u>: 100 mg (2.5 mL) twice a day on the first day.
<u>Maintenance dose</u>: 100 mg (2.5 mL) once a day for 13 days.</td></tr>
<tr><td>OPC Refractory (rOPC) to Itraconazole and/or Fluconazole</td><td>Oral Suspension: 400 mg (10 mL) twice a day. Duration of therapy is based on the severity of the patient’s underlying disease and clinical response.</td></tr>
</table></td></tr>
</table>

	Pediatrics: For pediatric patients 2 to less than 18 years of age; for prophylaxis of invasive Aspergillus and Candida infections: - weighing less than or equal to 40 kg: (b) (4) • delayed-release tablet: 300 mg twice daily on the first day; 300 mg once daily thereafter. - regardless of body weight: • injection: 6 mg/kg up to a maximum of 300 mg twice daily on the first day; 6 mg/kg up to a maximum of 300 mg once daily thereafter. For pediatric patients 13 to less than 18 years of age, for: - prophylaxis of invasive Aspergillus and Candida infections: • oral suspension: 200 mg (5 mL) three times a day. Duration of therapy is based on recovery from neutropenia or immunosuppression. - treatment of oropharyngeal candidiasis (OPC): • oral suspension: 100 mg (2.5 mL) twice daily on the first day; 100 mg (2.5 mL) once daily for 13 days. - treatment of OPC Refractory (rOPC) to itraconazole and/or fluconazole oral suspension: • oral suspension: 400 mg (10 mL) twice daily. Duration of therapy is based on the severity of the patient's underlying disease and clinical response.
How Supplied	Injection: single-dose Type I glass vials Delayed-Release Tablets: Bottles with child-resistant closures of 60 delayed-release tablets Oral Suspension: 4-ounce (123 mL) amber glass bottles with child-resistant closures containing 105 mL of suspension (40 mg of posaconazole per mL). Supplied with each oral suspension bottle is a plastic dosing spoon calibrated for measuring 2.5-mL and 5-mL doses. For Delayed-Release Oral Suspension: Package A: a kit with 8 child-resistant single-use packets of Noxafil Powder 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.
Storage	Injection: [redacted] (b) (4) vial should be stored refrigerated at 2-8°C (36-46°F). Once admixed, the product should be used immediately. If not used immediately, the solution can be stored up to 24 hours refrigerated 2-8°C (36-46°F). Delayed-Release Tablets, oral suspension: controlled room temperature For delayed-release oral suspension: 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 the powder for delayed-release oral suspension until ready for use. The reconstituted suspension must be used within 1 hour. Discard unused portion of the prepared drug product.
Container Closure/Device Constituent	For Delayed-Release Oral Suspension: Package A: a kit with 8 child-resistant single-use packets of Noxafil Powder 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.
Intended Users	Caregivers, nurses, pharmacists
Intended Use Environment	Home and clinical environments

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On December 7, 2020, we searched the L:drive and AIMS using the terms, "posaconazole," "125097," and "Noxafil" to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified fifteen previous reviews[17,18,19,20,21,22,23,24,25,26,27,28,29,30,31], and we confirmed that our previous recommendations were implemented or considered.

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[17] Myers, D. Label and Labeling Review for Noxafil (NDAs 022003/S-026, 205053/S-010, and 205596/S-010).). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 15. RCM No. 2020-819.

[18] Purcell, J. Human Factors Memorandum for Noxafil (IND 125097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 15. RCM No.: 2019-264-1.

[19] Purcell, J. Human Factors Validation Study Protocol for Noxafil (IND 125097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 12. RCM No.: 2019-264.

[20] Myers, D. Postmarket Medication Error Review for Noxafil (NDA 205053). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 09. RCM No.: 2017-354.

[21] Sheppard, J. Postmarket Medication Error Memo for Noxafil (NDAs 022003, 022027, and 205053). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 DEC 16. RCM No.: 2014-2597-03.

[22] Sheppard, J. Label and Labeling Review Memo for Noxafil (NDAs 022003, 022027, 205053, and 205596). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 NOV 10. RCM No.: 2014-2597-02.

[23] Sheppard, J. Label and Labeling Review for Noxafil (NDA 205596/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 SEP 25. RCM No.: 2015-1725.

[24] Sheppard, J. Label and Labeling Review Memo for Noxafil (NDAs 022003, 022027, 205053, and 205596). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 JUN 22. RCM No.: 2014-2597-01.

[25] Sheppard, J. Medication Error Postmarket Review for Noxafil (NDAs 022003, 022027, 205053, and 205596). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAR 18. RCM No.: 2014-2597.

[26] Sheppard, J. Label and Labeling Review Memo for Noxafil (NDAs 022003 and 022027). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAR 10. RCM No.: 2008-776-01.

[27] Chan, I. Post Marketing Review for Noxafil (NDAs 022003 and 022027). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 NOV 01. RCM No.: 2008-776.

[28] Kapoor, R. Label and Labeling Review for Noxafil (NDA 205596). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 FEB 07. RCM No.: 2013-2518.

[29] Winiarski, A. Label and Labeling Review for Noxafil (NDA 205053). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 SEP 25. RCM No.: 2013-777.

[30] Mahmud, A. Proprietary Name Review for Noxafil (NDAs 022003 and 022027). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2006 AUG 29. RCM No.: 2006-90.

[31] Bridges, T. Label and Labeling Review for Noxafil (NDAs 022003 and 022027). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2006 MAR 27. RCM No.: 2004-0028-2.

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APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The HF validation study protocol is accessible in EDR via:
\\cdsesub1\evsprod\ind125097\0026\m1\us\meeting-req-appendix-1.pdf

The Task Analysis and Use Error Analysis can be accessed in EDR via:
\\CDSESUB1\evsprod\nda214770\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\peds\5354-other-stud-rep\05h9b0\05h9b0.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessed in EDR via:
\\CDSESUB1\evsprod\nda214770\0028\m5\53-clin-stud-rep\535-rep-effic-safety-stud\peds\5354-other-stud-rep\05h99z\06cgkm.pdf

Table 19. Summary of post-validation changes

Summary of post-validation change	Rationale for change	Rationale why re-validation is not required
1. The PI will include dosing information	The PI includes a dose reference table and associated explanation to mitigate the risk that a user may attempt to administer the complete sachet of suspension instead of a specific proportion required for the prescribed dose. Although volumetric dosing is fundamental to the operating principle of oral suspensions, including a dose reference table will assist pharmacists will be able to have a better understanding of the preparation process.	It is determined that the changes described are not applicable to require re-validation as the dosing table was not subject to HF Validation as it is presented in the PI. The dosing information is also a standard and required element of the PI. The change is relevant to the medical labeling intended for use by healthcare professionals.
2. The PI will include information about the special design of the notched-tip syringes	Due to the proportion of participants that thought it was acceptable to use other oral syringes for preparing and administering the suspension, information included in the PI shall explain to healthcare professionals why the provided oral syringe is different (notched tip) and why it should not be substituted with a standard oral syringe. The updated information in the PI will also include information about the risk of using regular syringe (i.e. aggregation).	It is determined that the changes described are not applicable to require re-validation as the information about the notched-tip syringe was not subject to HF Validation because it is presented in the PI. The dosing and administration information is also a standard and required element of the PI. The change is relevant to the medical labeling intended for use by healthcare professionals. In addition, the risk of using regular syringe has been captured and analyzed in risk management file.
3. Additional spare Noxafil oral syringes will be provided	Spare oral syringes are planned to be provided in a separate carton due to a study finding that some clinical institutions policies prohibit re-use of oral syringes. Providing a carton of additional oral syringes is intended to minimize the likelihood that healthcare professionals choose to use alternative oral syringes to prepare and administer the Noxafil oral suspension.	It is determined that re-validation is not necessary as: • The Noxafil presentation validated in the study has not changed. • The oral syringes planned to be provided to users are identical to those provided in the carton and tested in the HF Validation study. • The way in which the spare syringes are being used is not changed versus that tested in HF Validation. • There are no foreseeable use related risks resulting from provision of spare syringes.

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

We sent an Information Request (IR) to Merck on October 15, 2020 to clarify the HF validation study results. The IR responses can be accessed in EDR via:

\\CDSESUB1\evsprod\nda214770\0006\m1\us\quality-information-amendment-29oct2020-1.pdf

\\CDSESUB1\evsprod\nda214770\0006\m1\us\quality-information-amendment-29oct2020-2.pdf

\\CDSESUB1\evsprod\nda214770\0006\m1\us\quality-information-amendment-29oct2020-3.pdf

\\CDSESUB1\evsprod\nda214770\0006\m1\us\quality-information-amendment-29oct2020-4.pdf

We sent an IR to Merck on December 10, 2020 to request images of the prescription orders that were reviewed by caregiver, nurse, and pharmacist participants in the HF validation study. The IR response can be accessed in EDR via:

\\CDSESUB1\evsprod\nda214770\0009\m1\us\quality-information-amendment-14dec2020.pdf

We sent an IR to Merck on March 4, 2021 to request specific details regarding use errors that occurred during the HF study. The IR responses can be accessed in EDR via:

\\CDSESUB1\evsprod\nda214770\0021\m1\us\quality-information-amendment-12mar2021-5.pdf

\\CDSESUB1\evsprod\nda214770\0021\m1\us\quality-information-amendment-12mar2021-6.pdf

We sent an IR to Merck on April 28, 2021 to request more detailed information regarding their proposed postmarket commitment (PMC) for dosing pediatric patients who weigh > 40 kg. The IR response can be accessed in EDR via:

\\CDSESUB1\evsprod\nda214770\0031\m1\us\quality-information-amendment-30apr2021.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[32] along with postmarket medication error data, we reviewed the following posaconazole labels and labeling submitted by Merck.

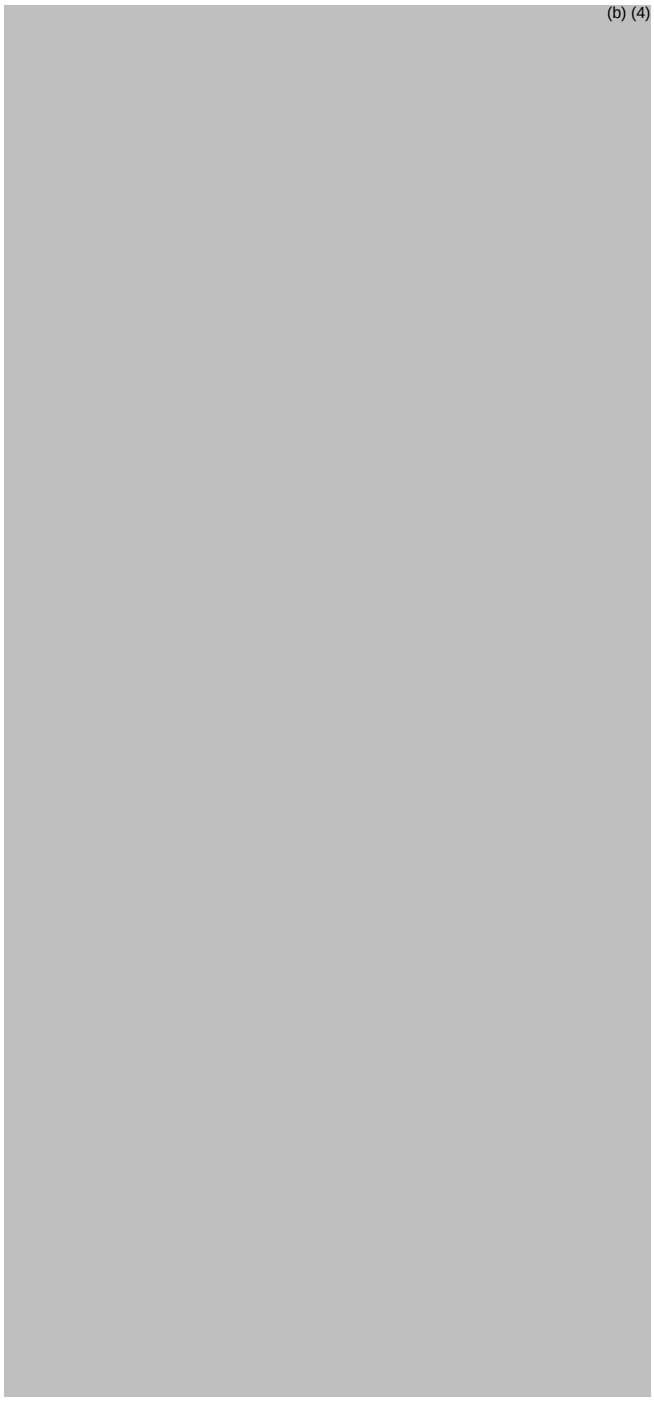
- Container (sachet) label received on February 12, 2021
- Mixing liquid label received on February 12, 2021
- Package A: Carton labeling received on February 12, 2021
- Package B: Carton labeling for syringes received on February 12, 2021
- Noxafil oral suspension Carton labeling received on February 12, 2021
- Instructions for Use received on February 12, 2021
    - \\CDSESUB1\evsprod\nda205596\0108\m1\us\03-wrm-ifu-mk5592-pediatric-pfs.doc
- Patient Information received on February 12, 2021
    - \\CDSESUB1\evsprod\nda205596\0108\m1\us\03-wrm-usppi-mk5592-mf-pediatric-pfs.doc
- Prescribing Information for NDA 205596 S-012 (Image not shown) received on February 12, 2021
    - \\CDSESUB1\evsprod\nda205596\0108\m1\us\03-wrm-uspi-mk5592-mf-pediatric-pfs.doc
- Prescribing Information for NDA 205596 S-013 (Image not shown) received on August 19, 2020
    - \\CDSESUB1\e+sprod\nda205596\0102\m1\us\02-wrm-uspi-mk5592-mf-p069.doc

[32] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

F.2 Label and Labeling Images

Container (sachet) label

(b) (4)



4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CAMERON D JOHNSON
05/13/2021 11:12:30 AM

EBONY A WHALEY
05/13/2021 11:16:25 AM

LOLITA G WHITE
05/13/2021 02:57:39 PM

MISHALE P MISTRY on behalf of IRENE Z CHAN
05/13/2021 03:20:43 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 22, 2021

To: Amy Bishara, M.D.
Division of Anti-Infectives (DAI)

Christopher Smith, Regulatory Project Manager, DAI

Abimbola Adebowale, Associate Director for Labeling, DAI

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for NOXAFIL (posaconazole) injection, for intravenous use, NOXAFIL (posaconazole) delayed-release tablets, for oral use, NOXAFIL (posaconazole) oral suspension, and NOXAFIL (posaconazole) powder for delayed-release oral suspension

NDA: 214770, 205596/Supplement 012, and 205053/ Supplement 12

In response to DAI's consult request dated April 6, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI)/Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Noxafil. This supplement (S012) adds an indication in children and adolescents (aged 2 to <18 years) for prophylaxis of invasive Aspergillus and Candida infections in 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.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAI on April 13, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI/IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on April 15, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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/s/

DAVID F FOSS
04/22/2021 08:49:50 PM