CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212156Orig1s000

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:	March 15, 2021
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 212156
Product Name and Strength:	Micafungin for Injection, 50 mg/vial and 100 mg/vial
Applicant/Sponsor Name:	Par Sterile Products, LLC (Par)
OSE RCM #:	2021-446
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader (Acting):	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

On December 21, 2020, Par submitted their Class 2 Resubmission to provide their responses to the deficiencies included in the Agency's Complete Response Letter (CRL), dated May 18, 2020.[a] Thus, the Division of Anti-Infectives (DAI) requested that we review the proposed prescribing information (PI), container label, and carton labeling for Micafungin (Appendix A) to determine if they are acceptable from a medication error perspective.

2 DISCUSSION

Prior to the issuance of the May 18, 2020 CRL, we reviewed the Micafungin prescribing information, container labels, and carton labeling. Par's resubmission includes both draft and annotated prescribing information (PI), as well as container labeling identical to that included in their submission dated April 10, 2020.[b] Additionally, included in their Complete Response

[a] Zuffova, E. Communication: Complete Response Letter for Micafungin for Injection. Silver Spring (MD): FDA, CDER, OND, OAP, DAI (US); 2020 MAY 18. NDA 212126. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80565a78&_afrRedirect=486932362470892.

[b] Revised Vial Labels Received on April 10, 2020 (Micafungin NDA 212156) Chestnut Ridge (NY): Par Sterile Products, LLC; 2020 APR 10. Available from: \\CDSESUB1\evsprod\nda212156\0015\m1\us\draft-vial-labels.pdf.

dated December 21, 2020,[c] Par cross-references carton labeling included in their submission dated April 6, 2020.[d] We previously found the proposed container labels and carton labeling acceptable.[e,f] Additionally, we note that our previous recommendations to DAI[g] have been implemented in the PI received on December 21, 2020.

3 CONCLUSION

Our evaluation of the proposed micafungin prescribing information (PI) and container labels included in the resubmission dated December 21, 2020, and carton labeling included in the submission dated April 6, 2020, did not identify additional areas of vulnerability that may lead to medication errors. Therefore, we have no additional recommendations at this time.

[c] Complete Response received on December 21, 2020 (Micafungin NDA 212156) Chestnut Ridge (NY): Par Sterile Products, LLC; 2020 DEC 21. Available from: \\CDSESUB1\evsprod\nda212156\0016\m1\us\complete-response.pdf.

[d] Revised Cartons Received on April 6, 2020 (Micafungin NDA 212156) Chestnut Ridge (NY): Par Sterile Products, LLC; 2020 APR 06. Available from: \\CDSESUB1\evsprod\nda212156\0014\m1\us\draft-cartons.pdf.

[e] Myers D. Label and Labeling Review Memo for Micafungin (NDA 212156). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 09. RCM No.: 2018-2529-1.

[f] Myers D. Label and Labeling Review Memo for Micafungin (NDA 212156). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 22. RCM No.: 2018-2529-2.

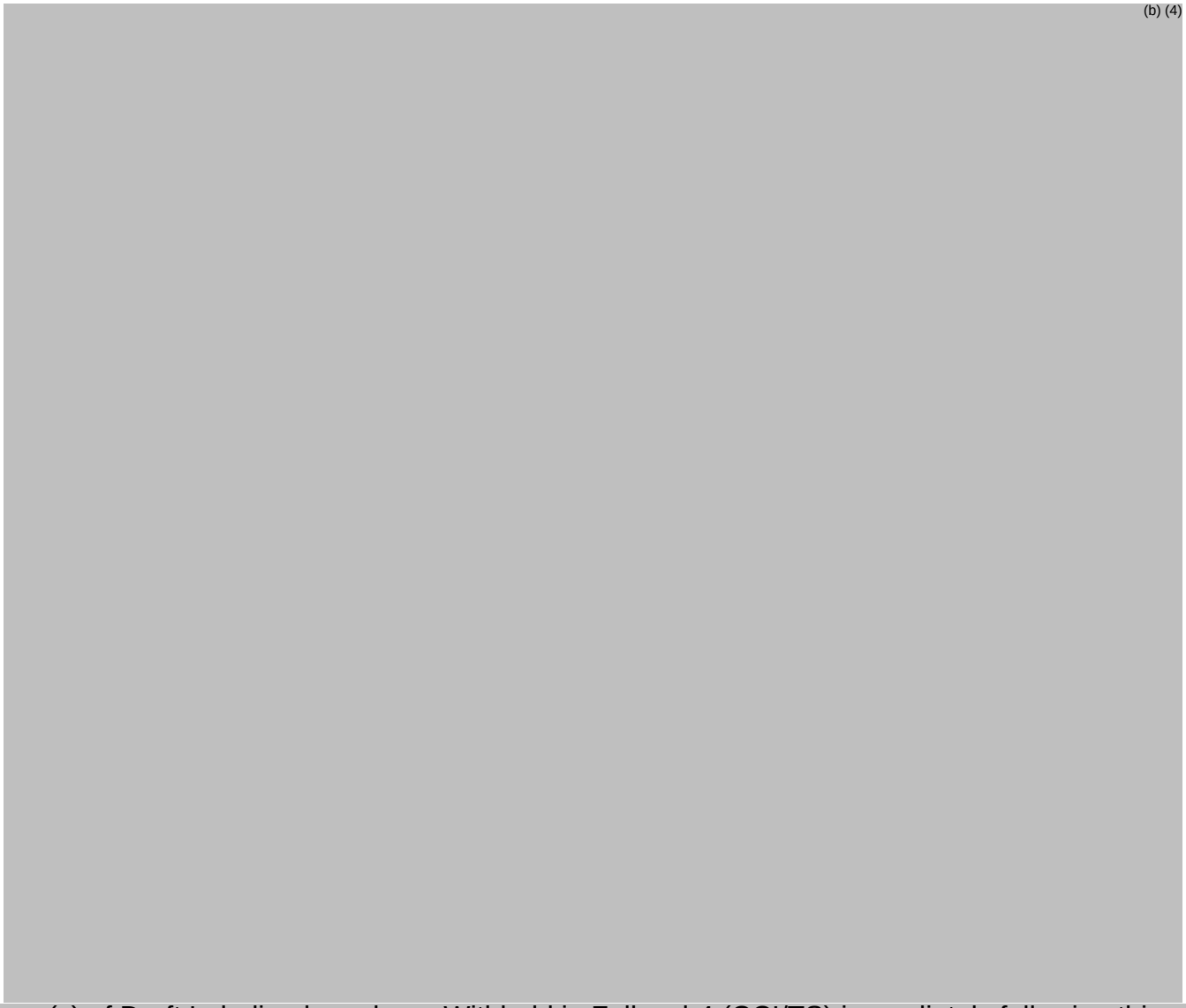
[g] Myers, D. Label and Labeling Review for Micafungin (NDA 212125). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 25. RCM No.: 2018-2529.

APPENDIX A. IMAGES OF LABEL AND LABELING

Prescribing Information (PI) received on December 21, 2020 (image not shown):

- Clean proposed (Draft) PI available at the following link: \\CDSESUB1\evsprod\nda212156\0016\m1\us\micafungin-package-insert.doc.
- Annotated PI available at the following link: \\CDSESUB1\evsprod\nda212156\0016\m1\us\micafungin-insert-tc-feb-2020.doc.

Container labels received on December 21, 2020



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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics, Urology, and Reproductive Medicine
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

MEMORANDUM TO FILE

From: Ramy Abdelrahman, MD, Clinical Reviewer
Division of Pediatric and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
John J. Alexander, MD, MPH, Deputy Division Director
DPMH, ORPURM, OND

To: Division of Anti-Infectives (DAI)

Drug: Micafungin for Injection, 50 mg/vial and 100 mg/vial

NDA: 212156

Sponsor: Par Sterile Products, LLC

Proposed Indication:

- Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses in adult and pediatric patients 4 months of age and older.
- Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses ***without*** meningoencephalitis and/or ocular dissemination in pediatric patients 4 months of age.
- Treatment of Esophageal Candidiasis in adult and pediatric patients 4 months of age and older.
- Prophylaxis of *Candida* Infections in adult pediatric patients 4 months of age and older undergoing Hematopoietic Stem Cell Transplantation (HSCT).

Materials reviewed:

- 2/10/20 Applicant's proposed labeling in DARRTS under NDA 212156
- Mycamine NDA 021506 Supplement 23, and Supplement 19 labeling.[1,2]

Consult Request:

DAI consulted DPMH to assist with the review of the proposed pediatric use information in labeling for this 505(b)(2) new drug application (NDA) as it relates to FDARA.

Background:

The Applicant, Par Sterile Products, LLC, submitted NDA 212156 as a 505(b)(2) application which is relying on FDA's previous findings of safety and efficacy of the listed drug (LD), Mycamine (NDA 021506). The Orange Book reflects that Mycamine was granted 3 years of Hatch-Waxman marketing exclusivity (I-821) under 21 CFR 314.108 in addition to 6-month pediatric exclusivity (I-821*PED) under the Best Pharmaceuticals for Children Act (BCPA) due to the recent FDA approval of supplemental NDA (S-023) on 12/20/2019. The exclusivity will expire on 06/20/2023.

DAI approved Supplement 23 for the LD on the basis of the following: (1) a phase 3 trial comparing a 21-day regimen of micafungin 10 mg/kg/day to amphotericin B 1 mg/kg/day in patients younger than 4 months with candidemia, acute disseminated candidiasis, and suspected meningoencephalitis that was terminated early due to low enrollment; (2) data from two Italian investigator-initiated open-label phase 2 studies of micafungin in neonates and young infants with invasive candidiasis and Candida meningoencephalitis to which the Applicant had right of reference. Approval of this Supplement led to the addition of the following indication to the Mycamine prescribing information:

- Treatment of candidemia, acute disseminated candidiasis, Candida peritonitis and abscesses without meningoencephalitis and/or ocular dissemination in pediatric patients younger than 4 months of age

Protected pediatric use information was added to the following sections of micafungin for injection labeling:

- Highlights
- Indications and Usage (Section 1)
- Dosage and Administration: (b) (4)
- Adverse Reactions: Clinical Trials Experience (Subsection 6.1)
- Use in Specific Populations: Pediatric Use (Subsection 8.4)
- Overdosage (Section 10)
- Clinical Pharmacology: Pharmacokinetics (Subsection 12.3)

[1] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021506s023lbl.pdf
[2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021506s019lbl.pdf

Pediatric Research Equity Act (PREA)
The proposed 505(b)(2) NDA for Micafungin for Injection doesn't trigger PREA because the application does not provide a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration of micafungin for injection when compared to the LD, Mycamine. The only difference between the Applicant's proposed product and the LD, is that the proposed drug product contains a non-exception excipient not present in the LD.

Federal Reauthorization Act of 2017 (FDARA)
505A(o)(l) & (2) state:
PROMPT APPROVAL OF DRUGS WHEN PEDIATRIC INFORMATION IS ADDED TO LABELING.—
"(1) GENERAL RULE.—A drug for which an application has been submitted or approved under subsection (b)(2) or (j) of section 505 shall not be considered ineligible for approval under that section or misbranded under section 502 on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication or other aspect is protected by patent, or by exclusivity under clause (iii) or (iv) of section 505(j)(5)(F), clause (iii) or (iv) of section 505(c)(3)(E), or section 527(a), or by an extension of such exclusivity under this section or section 505E."
"(2) LABELING.— Notwithstanding clauses (iii) and (iv) of section 505(j)(5)(F), clauses (iii) and (iv) of section 505(c)(3)(E), or section 527, the Secretary may require that the labeling of a drug approved pursuant to an application submitted under subsection (b)(2) or (j) of section 505 that omits a pediatric indication or other aspect of labeling as described in paragraph (1) include — ''(A) a statement that, because of marketing exclusivity for a manufacturer — ''(i) the drug is not labeled for pediatric use; or ''(ii) in the case of a drug for which there is an additional pediatric use not referred to in paragraph (1), the drug is not labeled for the pediatric use under paragraph (1); and ''(B) a statement of any appropriate pediatric contraindications, warnings, precautions, or other information that the Secretary considers necessary to assure safe use."

DPMH Summary:

- *This drug is relying on FDA's previous findings of safety and efficacy of Mycamine (NDA 021506). Currently, the approval for use of Mycamine for the treatment of candidemia, acute disseminated candidiasis, Candida peritonitis and abscesses without meningoencephalitis and/or ocular dissemination in pediatric patients younger than 4 months of age is protected by pediatric exclusivity.*
- *Pediatric use information pertaining to pediatric patient younger than 4 months of age can be carved out of the proposed product's labeling without rendering this product less safe or effective for remaining non-protected conditions of use with the exception of the following changes:*
    - *The DAI identified that the data from the "11 clinical trials" described under "Clinical Trial Experience in Pediatric Patients" in subsection 6.1 of Mycamine labeling were different from the 11 clinical trials described*

in Supplement 19 and included patients 4 months of age and older from two of the new studies submitted to Supplement 23. Therefore, DAI in discussion with DPMH and OCC decided to restore the number of patients and corresponding percentages of demographic and adverse event information that had been added to labeling in 2016 after approval of Supplement 19.

- *DAI, DPMH, and OCC agreed that data from the rabbit model described under subsection 8.4 was not protected and could be retained except for the following sentence, "Data from the rabbit model suggest that a micafungin dose regimen of 4 mg/kg once daily is inadequate to treat meningoencephalitis and that a dose regimen of approximately 10 to 25 mg/kg once daily may be necessary to lower fungal burden in the CNS in pediatric patients younger than 4 months of age" which implies how the rabbit dose could be applied to the dose for pediatric patients younger than 4 months.*

- *After expiration of pediatric exclusivity for the LD, the Applicant should be encouraged to add the carved-out labeling language so that the product will be adequately labeled for pediatric use.*
- *The following disclaimer language was agreed upon:*

Additional pediatric use information is approved for Astellas Pharma US, Inc.'s Mycamine® (micafungin for injection). However, due to Astellas Pharma US., Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

DPMH concurs with the model labeling for Micafungin for Injection that carves out exclusivity-protected information. DPMH concludes that this b2 labeling would not be less safe or effective than Mycamine for the remaining non-protected conditions of use.

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/s/

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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:	April 22, 2020
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 212156
Product Name and Strength:	Micafungin for Injection, 50 mg/vial and 100 mg/vial
Applicant/Sponsor Name:	Par Sterile Products, LLC (Par)
OSE RCM #:	2018-2529-2
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on April 10, 2020, for Micafungin. The Division of Anti-Infectives (DAI) requested that we review the revised container labels for Micafungin (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]

2 CONCLUSION

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

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[a] Myers D. Label and Labeling Review Memo for Micafungin (NDA 212156). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 09. RCM No.: 2018-2529-1.

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

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

Memorandum

Date: April 10, 2020

To: Ramya Gopinath, M.D.
Division of Anti-Infective Products (DAIP)

Eva Zuffova, Regulatory Project Manager, DAIP

Abimbola Adebowale, Associate Director for Labeling, DAIP

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

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for MICAFUNGIN for Injection, for intravenous use

NDA: 212156

In response to DAIP's consult request dated March 9, 2020, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Micafungin.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAIP on April 6, 2020, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling by electronic mail from DAIP on April 7, 2020, 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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DAVID F FOSS
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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:	April 9, 2020
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 212156
Product Name and Strength:	Micafungin for Injection, 50 mg/vial and 100 mg/vial
Applicant/Sponsor Name:	Par Sterile Products, LLC (Par)
OSE RCM #:	2018-2529-1
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on April 6, 2020 for Micafungin. The Division of Anti-Infectives (DAI) requested that we review the revised container labels and carton labeling for Micafungin (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]

2 CONCLUSION

The revised container labels are unacceptable from a medication error perspective. The statement "Discard Unused Portion" is (b) (4) on the revised container labels. Below we provide our recommendation to delete the occurrence of the statement "Discard Unused Portion" that is currently located below "contains XX mg micafungin" and above the line "For Intravenous Infusion Only".

3 RECOMMENDATIONS FOR PAR STERILE PRODUCTS, LLC

As currently presented, the statement "Discard Unused Portion" is (b) (4) on your revised container labels. The intent of our previous recommendation *"To improve clarity and*

[a] Myers, D. Label and Labeling Review for Micafungin (NDA 212156). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 25. RCM No.: 2018-2529.

readability, consider moving [redacted] (b) (4) *on the PDP by relocating the currently bolded statement "Discard unused portion." to follow the package type term "Single-Dose Vial.""* was that subsequent to the relocation of the statement "Discard Unused Portion" from below "contains XX mg micafungin" and above the line "For Intravenous Infusion Only", that the statement "Discard Unused Portion" would be deleted. Therefore, to eliminate the [redacted] (b) (4) the statement "Discard Unused Portion" on the revised container labels, delete the occurrence of the statement "Discard Unused Portion" that is currently below "contains XX mg micafungin" and above the line "For Intravenous Infusion Only".

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LABEL 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:	March 25, 2020
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 212156
Product Name and Strength:	Micafungin for Injection, 50 mg/vial and 100 mg/vial
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Par Sterile Products, LLC (Par)
FDA Received Date:	November 19, 2018, July 18, 2019, and February 10, 2020
OSE RCM #:	2018-2529
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF REVIEW VS REASON FOR REVIEW

As part of the approval process for Micafungin for Injection, 50 mg/vial and 100 mg/vial, the Division of Anti-Infectives (DAI) requested that we review the proposed container labels, carton labeling, and prescribing information for areas that may lead to medication errors.

2 REGULATORY HISTORY

On November 19, 2018, Par submitted an original New Drug Application (NDA 212156) for Micafungin for Injection, 50 mg/vial and 100 mg/vial, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA). The listed drug (LD) product is Mycamine, NDA 021506

On January 18, 2019, the Agency sent Par a Refuse to File (RTF) letter informing them that their application was not sufficiently complete to permit a substantive review.

On July 18, 2019, Par resubmitted NDA 212156 along with their complete response to the Agency's major deficiency comment. In their resubmission, a labeling summary was provided referencing the container label and carton labeling previously submitted on November 19, 2018.

On February 10, 2020, in response to the Agency's Information Request (Labeling) dated January 30, 2020, Par submitted their revised prescribing information (PI) labeling to be consistent with the most recently approved labeling for Mycamine (approved December 20, 2019).

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted container labels, carton labeling, and prescribing information, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Anti-Infectives (DAI)

Prescribing Information			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	As currently presented, there are inconsistencies between the February 10, 2020, revised prescribing information (PI) and the most recently approved listed drug (LD) labeling for Mycamine (approved December 20, 2019).	Inconsistent labeling may contribute to confusion that can result in medication error.	In the *Highlights of Prescribing Information*, under *Indications and Usage*, the first sentence currently is, (b) (4) the first sentence should instead be "Micafungin for injection is an echinocandin indicated in adult and pediatric patients for (1):" (b) (4)

			(b) (4) [redacted] In the Highlights of Prescribing Information, under *Indications and Usage*, (b) (4) [redacted] includes the text, "Prophylaxis of *Candida* Infections in adult pediatric patients 4 months…" In comparison the Mycamine PI, includes "…adult and pediatric patients…" To align with the Mycamine PI the forth bullet should instead be "Prophylaxis of *Candida* Infections in adult and pediatric patients 4 months…"
Full Prescribing Information – Section 16, *How Supplied/Storage and Handling*			
1.	We note the inclusion of the statement, "The vial stopper is not (b) (4) [redacted] with natural rubber latex." We defer to the OPQ for their assessment and to determine if the statement "The vial stopper is not (b) (4) [redacted] with natural rubber latex." is appropriate.		
Container Label and Carton Labeling			

1.	We note the inclusion of the statement, "The vial stopper is not made with natural rubber latex." We defer to the OPQ for their assessment and to determine if the statement "The vial stopper is not made with natural rubber latex." is appropriate.

Table 3: Identified Issues and Recommendations for Par Sterile Products, LLC (entire table to be conveyed to Applicant)

Container Labels and Carton Labeling			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	As currently presented, the "(b) (4)" is included on the container labels and "(b) (4)" on the carton labeling.	Since dosage form for this product is "for injection" (i.e., lyophilized powder) the inclusion of "(b) (4)" could cause confusion. Also, users may misinterpret and think that (b) (4) resulting in wrong technique preparation medication errors.	Remove "(b) (4)" from the container labels and carton labeling. For example, the carton labeling text should be "10 Single-Dose Vials."
Container Labels			
1.	As currently presented, the format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the 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.
2.	As currently presented, the package type term, "Single-Dose Vial" and the statement "Discard Unused Portion" are included on the principal display panel (PDP) of the label, however in separate areas.	Since any contents remaining in a single dose vial should be discarded, locating these statements together addresses the risk that this important information could be overlooked or missed resulting in the use of potentially contaminated product.	To improve clarity and readability, consider moving these statements together on the PDP by relocating the currently bolded statement "Discard unused portion." to follow the package type term "Single-Dose Vial." For example, "Single-Dose Vial – Discard Unused Portion."
Carton Labeling			
1.	As currently presented, the intended location for the lot number and expiration date is not provided on the proposed carton labeling that was submitted.	The lot number statement is required on the carton labeling per 21 CFR 201.10(i)(1) and the product expiration date is also required on the carton labeling per 21 CFR 201.17.	Include the space notation for the lot number statement and expiration date. When determining this placement, please ensure that there are no other numbers located in close proximity to the lot number/expiration date that can be mistaken as the lot number/expiration date. Additionally, to minimize confusion and reduce the risk

			for deteriorated drug medication errors, identify the format you intend to use. We recommend that the human-readable expiration date on the container labels and carton labeling 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.
2.	As currently presented, the intended location of the human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the carton) is not provided.	The drug package label must include the product identifier information (i.e., the NDC, serial number, lot number, and expiration date) in both the human-readable form and machine-readable, 2D data matrix barcode format.	We recommend you include the intended location of the machine-readable, 2D data matrix barcode product identifier, near the human-readable portion of the product identifier information (i.e., NDC: [insert product's NDC] SERIAL: [insert product's serial number] LOT: [insert product's lot number]

			EXP: [insert product's expiration date]). See draft guidance https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf (Lines 255 - 283).

5 CONCLUSION

Our evaluation of the proposed container labels, carton labeling and prescribing information identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Par so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for micafungin that Par submitted on November 19, 2019, and the listed drug (LD), Mycamine (NDA 021506).

Table 4. Relevant Product Information for Listed Drug and micafungin		
Product Name	Mycamine (NDA 021506)	micafungin
Initial Approval Date	March 16, 2005	N/A
Active Ingredient	micafungin	micafungin
Indication	For adult and pediatric patients for: • Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses in adult and pediatric patients 4 months of age and older • Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses ***without*** meningoencephalitis and/or ocular dissemination in pediatric patients younger than 4 months of age • Treatment of Esophageal Candidiasis in adult and pediatric patients 4 months of age and older • Prophylaxis of *Candida* Infections in adult and pediatric patients 4 months of age and older undergoing Hematopoietic Stem Cell Transplantation (HSCT)	For adult and pediatric patients for: • Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses in adult and pediatric patients 4 months of age and older (b) (4) [redacted] • Treatment of Esophageal Candidiasis in adult and pediatric patients 4 months of age and older • Prophylaxis of *Candida* Infections in adult pediatric patients 4 months of age and older undergoing Hematopoietic Stem Cell Transplantation (HSCT)

<table>
<tr><td>Route of Administration</td><td>Intravenous infusion</td><td>Intravenous infusion</td></tr>
<tr><td>Dosage Form</td><td>Sterile lyophilized powder for injection</td><td>Sterile lyophilized powder for injection</td></tr>
<tr><td>Strength</td><td>50 mg single-dose vial
100 mg single-dose vial</td><td>50 mg single-dose vial
100 mg single-dose vial</td></tr>
<tr><td>Dose and Frequency</td><td>Recommended Dosage Administered by Indication, Weight and Age (2.1, 2.2, 2.3, 8.4)
<table>
<tr><th>Adult</th><th>Pediatric Patients 4 Months and Older 30 kg or less</th><th>Pediatric Patients 4 Months and Older greater than 30 kg</th><th>Pediatric Patients Younger than 4 Months of Age</th></tr>
<tr><td colspan="4">Treatment of Candidemia, Acute Disseminated Candidiasis, Candida Peritonitis and Abscesses</td></tr>
<tr><td>100 mg daily</td><td colspan="2">2 mg/kg/day (maximum 100 mg daily)</td><td>See below</td></tr>
<tr><td colspan="4">Treatment of Candidemia, Acute Disseminated Candidiasis, Candida Peritonitis and Abscesses <u>without</u> Meningoencephalitis and/or Ocular Dissemination</td></tr>
<tr><td>See above</td><td colspan="2">See above</td><td>4 mg/kg/day</td></tr>
<tr><td colspan="4">Treatment of Esophageal Candidiasis</td></tr>
<tr><td>150 mg daily</td><td>3 mg/kg/day</td><td>2.5 mg/kg/day (maximum 150 mg daily)</td><td>Not approved</td></tr>
<tr><td colspan="4">Prophylaxis of Candida Infections in HSCT Recipients</td></tr>
<tr><td>50 mg daily</td><td colspan="2">1 mg/kg/day (maximum 50 mg daily)</td><td>Not approved</td></tr>
</table></td><td>(b) (4)</td></tr>
<tr><td>How Supplied</td><td>Cartons of 10 individually packaged single-dose vials, coated with a light protective film and sealed with a flip-off cap.</td><td>Single-dose vials supplied in packages of 10.</td></tr>
<tr><td>Storage</td><td>Unopened vials of lyophilized material must be stored at room temperature, 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Store the reconstituted product at 25°C (77°F) [see Dosage and Administration (2.4)].
Store the diluted solution at 25°C (77°F) [see Dosage and Administration (2.4)].
Protect from light.</td><td>(b) (4)
Protect from light.</td></tr>
<tr><td>Container Closure</td><td>Sealed with a flip off cap: blue for 50 mg/vial and red for 100 mg/vial.</td><td>Glass Vial: 10 mL, 20 mm (b) (4)
(b) (4)
Elastomeric Closure: 20 mm, (b) (4)
<u>Flip-off cap</u>: Flip-off cap 20 mm (b) (4) (50 mg/vial)</td></tr>
</table>

		(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 11, 2020, we searched the L:drive and AIMS using the term, micafungin to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 2 previous reviews[a,b,c,d,e,f], that we reviewed to determine if our previous recommendations would be applicable to this review.

APPEARS THIS WAY ON ORIGINAL

[a] Winiarski, A. Label and Labeling Review for Mycamine (NDA 021506/S-015). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 APR 04. RCM No.: 2013-680.

[b] Kolejian, S. Label and Labeling Review Memo for Mycamine (NDA 021506/S-019). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 AUG 18. RCM No.: 2016-1843.

[c] Myers, D. Label and Labeling Review for Micafungin (NDA 212125). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 12. RCM No.: 2018-1726.

[d] Myers, D. Label and Labeling Review Memo for Micafungin (NDA 212125). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 08. RCM No.: 2018-1726-1.

[e] Myers, D. Label and Labeling Review for Mycamine (NDA 021506/S-023). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 10. RCM No.: 2019-1283.

[f] Myers, D. Label and Labeling Review Memo for Mycamine (NDA 021506/S-023). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 30. RCM No.: 2019-1283-1.

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,[g] along with postmarket medication error data, we reviewed the following micafungin labels and labeling submitted by Par on November 19, 2018 and February 10, 2020.

- Container labels submitted on November 19, 2018
- Carton labeling submitted on November 19, 2018
- Prescribing Information submitted on February 10, 2020, available at the following link: \\cdsesub1\evsprod\nda212156\0010\m1\us\micafungin-package-insert.doc

F.2 Label and Labeling Images

- Container labels (not to scale)

(b) (4)

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

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

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/s/

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