CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212156Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Combined Cross-Discipline Team Leader and Division Director Review

Date	April 20, 2020
From	Sumathi Nambiar MD MPH; Andrei Ponta, PhD
Medical Team Leader	Yuliya Yasinskaya M.D., MPH
Subject	Cross-Discipline Team Leader and Division Director Review
NDA #	212156
Applicant	Par Pharmaceuticals
Date of Submission	18-Jul-2019
PDUFA Goal Date	18-May-2020
Proprietary Name / Established (USAN) names	Micafungin for injection
Dosage forms / Strength	For injection: 50 mg single dose vial and 100 mg single dose vial
Proposed Indication(s)	Micafungin for injection is indicated 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
Regulatory Action	***Complete Response***

The submission is a 505(b)(2) New Drug Application for micafungin for injection available as 50 mg and 100 mg single dose vials. The Applicant submitted the information describing the chemistry, manufacturing and controls. The listed drug (LD) for this 505(b)(2) NDA is NDA 21506: Mycamine (micafungin for injection, for intravenous use).

The original NDA was submitted 19-Nov-2018 and the Agency determined that the NDA was not sufficiently complete to permit a substantive review due to lack of drug product stability data. Therefore, the NDA was not filed. A refuse to file letter was issued on 18-Jan-2019. The Applicant resubmitted the NDA on18-Jul-2019 with the appropriate amount of stability data.

The overall manufacturing inspection recommendation for this NDA was withhold as of 3-Apr-2020. The drug product facility has an acceptable history of lyophilization product

manufacture. The proposed drug substance intermediate manufacturer, (b) (4) (b) (4), was found unacceptable. The other sites are acceptable based on the previous inspection history (for additional details see the integrated quality review dated 10-Apr-2020).

There are several drug product issues that remain unresolved. These include inadequate or lack of justification for the drug product overfill, the analytical evaluation threshold (AET) used for the extractable/leachable study, the drug product release and stability impurity specifications, as well as outstanding concerns with the related substance and assay methods. In a response to an information request, the Applicant indicated that a response to all of the outstanding drug product issues would be submitted by 31-Jul-2020. As the PDUFA date for the NDA is 18-May-2020, the timeline proposed by the Applicant is not acceptable. This NDA is not recommended for approval from a drug product perspective (for additional details see the integrated quality review dated 10-Apr-2020).

The Applicant did not submit any new Pharmacology/Toxicology information in the NDA. However, Pharmacology/Toxicology is not recommending approval at this time due to unresolved issues regarding the leachables study and drug product impurity specifications (for additional details see the Pharmacology/Toxicology memo from Dr. Kelly Brant).

There were no Clinical Pharmacology, Clinical Microbiology, or Clinical/Statistical information/data submitted in this NDA; thus, no detailed discipline reviews were necessary.

Review of the Applicant's proposed label, packaging and product labeling was conducted by the DMEPA reviewer, Deborah Myers, RPh, MBA. The reviewer concluded that proposed label and labeling can be improved to decrease possible medication errors by removing the (b) (4) statement "Discard Unused Portion" (for specific recommendations to the Applicant see review dated 9-Apr-2020). The listed drug, Mycamine (NDA 21-506), received approval on 20-Dec-2019 to extend the indication of treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses to patients younger than 4 months of age (a new patient population); therefore, the labeling information supporting the use of Mycamine for this indication/population is protected by exclusivity and will be carved out from the labeling of generic micafungin products or any 505(b)(2) micafungin applications for 3 years since the time of approval. Specific sections affected by this carve out are: Indications and Usage (1), Dosage and Administration (2.2, 2.3), Adverse Reactions (6.1), Use in Specific Populations (8.4). The recommended carve out will be accompanied by the following statements: "*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"*

Recommendation

- Regulatory Action

  This NDA is recommended for a **Complete Response** from a chemistry, manufacturing, and controls (CMC) perspective. The overall manufacturing inspection recommendation

for this NDA was **Withhold**, as entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment on 3-Apr-2020. Additionally, the drug product review team determined the submission was **Inadequate** from a product quality perspective. The NDA will receive a complete response action at this time.

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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